FDA Executive Summary

Prepared for the
June 12, 2014 meeting of the
Circulatory System Devices Advisory Panel

P130024

Bard LUTONIX® 035 Drug Coated Balloon PTA Catheter

INTRODUCTION

This is the FDA Executive Summary for a first-of-a-kind drug coated peripheral percutaneous transluminal angioplasty (PTA) balloon, the LUTONIX® 035 Drug Coated PTA Balloon Catheter (referred to as LUTONIX DCB), indicated for use in the femoropopliteal arteries. This device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under Premarket Approval (PMA) application P130024, which is the subject of this Advisory Panel meeting.

This memorandum will summarize the FDA's review of the PMA up to this point, highlighting the particular areas for which we are seeking your expertise and input. These topics will include the proposed indications for use, pre-clinical study findings, the results from the randomized clinical study as well as the additional clinical studies conducted by the sponsor, and the proposed post-approval study. At the conclusion of your review and discussion of the data presented, the Agency will ask for your recommendation regarding whether or not the data demonstrate a reasonable assurance of safety and effectiveness.

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LIST OF ABBREVIATIONS

ABI - Ankle-Brachial Index
AE - Adverse Event
AT - As-treated
CEC - Clinical Events Committee
CRF - Case Report Form
DCB - Drug coated balloon
DUS - Duplex Ultrasound
Enrolled - Subjects are considered enrolled in the study after being consented and the defined pre-dilatation balloon inflation has begun. Not all enrolled subjects are randomized.
ITT - Intent-to-Treat
OUS - Outside the United States
PAD - Peripheral arterial disease
POBA- Plain Old Balloon Angioplasty
PP - Per-Protocol
PSVR - Peak Systolic Velocity Ratio
PTA - Percutaneous transluminal angioplasty
SAE - Serious Adverse Event
TLR - target lesion revascularization
TVR - target vessel revascularization

1 PROPOSED INDICATIONS FOR USE

The sponsor has proposed the following Indication for Use:

> "The LUTONIX® 035 Drug Coated Balloon PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive *de novo* or non-stented restenotic lesions (≤ 15 cm in length) in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm."

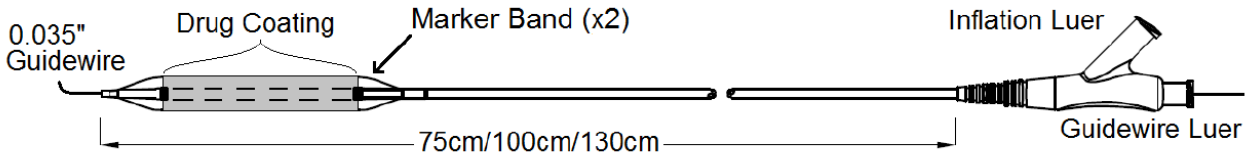
The clinical studies evaluating the LUTONIX® 035 Drug Coated Balloon PTA Catheter (LUTONIX DCB) were conducted using a treatment paradigm of pre-dilatation using an uncoated balloon catheter inflated to approximately 1mm less than the reference vessel diameter prior to use of the LUTONIX DCB. No data were presented to demonstrate how the Lutonix DCB would perform in the absence of pre-dilatation. Additionally, without pre-dilatation, the drug coating could potentially be disrupted when crossing tight lesions.

FDA Comment: The Panel will be asked to comment on whether the proposed Indications for Use statement is appropriate.

2 DEVICE DESCRIPTION

The LUTONIX DCB is a combination device/drug product incorporating an over-the-wire percutaneous transluminal angioplasty (PTA) catheter with paclitaxel drug coating on the surface of the balloon (see Figure 1).

Figure 1: LUTONIX 035 Drug Coated Balloon PTA Catheter, Model 9004



2.1 PTA Catheter Component

The LUTONIX DCB is compatible with a 0.035" guidewire and is available in 75 cm, 100 cm and 130 cm catheter lengths. Balloon sizes range from 4.0 mm - 6.0 mm in diameter and from 40 mm - 100 mm in length. Devices are compatible with 5F (for the 4.0-5.0 mm balloon diameters) and 6F (for the 6.0 mm balloon diameter) introducer sheaths (see Table 1). Note that all device sizes proposed for marketing were included in the clinical trials with exception of the 75 cm length catheter. The design of the LUTONIX DCB catheter component is similar to standard PTA catheters.

2.2 Drug Components

The LUTONIX DCB coating is a non-polymer based formulation, consisting of paclitaxel as

the active pharmaceutical ingredient and excipients polysorbate, sorbitol and methanol. The paclitaxel coating is distributed evenly across the working length of the balloon with a dose density of 2 µg/mm^2 yielding variable total dosage depending on balloon size (see Table 1).

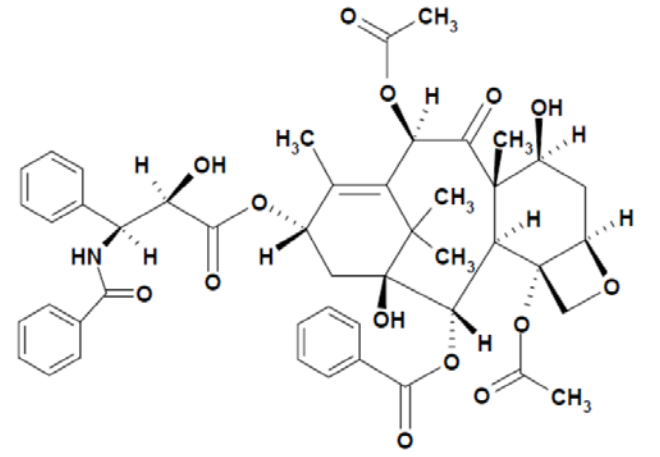
Table 1: LUTONIX 035 DCB PTA Device Sizes & Total Nominal Paclitaxel Dosage

Balloon Diameter (mm)	Paclitaxel Dose Density	Total Dosage (mg) per Balloon Length			
		40 mm	60 mm	80 mm	100 mm
4.0	2µg/mm^2	1.0	1.5	2.0	2.5
5.0		1.3	1.9	2.5	3.1
6.0		1.5	2.3	3.0	3.8

Paclitaxel is a cytotoxic drug used for oncological indications and manufactured using a semi-synthetic process (see Table 2: Paclitaxel Drug Details).

The excipients polysorbate, sorbitol, and methanol utilized in the Lutonix drug coating are as described in the USP National Formulary. The key functional characteristic of the excipients polysorbate and sorbitol in the formulation is to allow for adequate release of the paclitaxel drug substance to the tissue of the vascular wall during the balloon inflation. Methanol is used to dissolve the coating components and is subsequently removed during manufacturing.

Table 2: Paclitaxel Drug Details

Nomenclature	
United States Adopted Name (USAN)	Paclitaxel
Chemical Name	(2aR,4S,4aS,6R,7E,9S,11S,12S,12aR,12bS)-4,11-dihydroxy 4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-7,11-methano-1H-cyclodeca[[d]benzoxetine-6,9,12,12b-tetrayl 6, 12b-diacetate 12-benzoate 9 -[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate] or 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3- (benzoylamino)-2-hydroxy-3-phenylpropanoate]
CAS Registry Number	33069-62-4
Compendial Name (USP)	Paclitaxel
Structure	
Molecular Formula	C_{47} H_{51} NO_{14}
Relative Molecular Mass	Mr : 854
Structural Formula	

2.3 Mechanism of Action

The primary mode of operation for the LUTONIX DCB is the mechanical dilatation of the vessel, with the paclitaxel-based drug coating having an ancillary effect. The primary effect attributed to the device forms the basis for primary regulation under by the Center for Devices and Radiological Health (CDRH) with consultation from the Center for Drug Evaluation and Research (CDER). The mechanism by which neointimal growth is inhibited by the addition of the drug coating has not been established. In general, paclitaxel is a lipophilic anti-mitotic agent that prevents microtubule destruction, which has been reported in prior studies to prevent

migration/proliferation of smooth muscle cells, inflammatory cells and fibroblasts as well as inhibit the secretion of extracellular proteins. Several studies in animal models have also shown that paclitaxel applied locally reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia.[1, 2]

3 BACKGROUND INFORMATION AND REGULATORY HISTORY

Peripheral arterial disease (PAD) is estimated to be present in approximately 8 million people in the United States, including 12-20% of those individuals older than age 60.[3,4] The majority of PAD lesions are located in the femoropopliteal segment and, although some patients may be asymptomatic, some patients may have symptoms of claudication which may progress to critical limb ischemia. Management of these lesions had traditionally been surgical; however, endovascular treatment has become first line therapy for many patients. Endovascular treatment may include use of PTA alone or in association with stent placement and/or atherectomy. PTA alone is associated with high 12-month restenosis rates (often ≥60%), [5,6,7] and some first-generation stents were reported to have outcomes similar to PTA.[8,9] More recent stent designs, including an FDA approved drug-eluting stent, have improved 12-month restenosis rates (17% and 37%); [7,10,11,12]. However, restenosis remains a general concern and there is interest in non-permanent implant alternatives. For these reasons, the LUTONIX DCB was developed as a device-drug combination that is not a permanent implant, but aims to mitigate restenosis compared to PTA alone.

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[1] Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. J Clin Invest. 1995;95(4):1869-76.

[2] Axel DI, Kunert W, Göggelmann C et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997;96(2):636-45.

[3] Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. 2007 American Journal of Preventive Medicine 2007;32:328-333.

[4] Roger VL, Go AS, Lloyd-Jones DM, et. al. Heart Disease and Stroke Statistics 2011 Update: A Report From the American Heart Association. Circulation 2011;123:e18-e209.

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[6] Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Cath Cardiovasc Interv. 2007; 69:910-919.

[7] Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006; 354:1879-1888.

[8] Becquemin JP, Favre JP, Marzelle J, Nemoz C, Corsin C, Leizorovicz A. Systematic versus selective stent placement after superficial femoral artery balloon angioplasty: a multicenter prospective randomized study. J Vasc Surg. 2003; 37:487-494.

[9] Grimm J, Muller-Hülsbeck S, Jahnke T, Hilbert C, Brossmann J, Heller M. Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. J Vasc Interv Radiol. 2001; 12:935-942.

[10] Krankenberg H, Schlüter M, Steinkamp HJ, Bürgelin K, Scheinert D, Schulte KL, et al. Nitinol stent implantation versus percutaneous transluminal angioplasty in superficial femoral artery lesions up to 10 cm in length: the femoral artery stenting trial (FAST). Circulation. 2007;116:285-292.

[11] Bosiers M, Torsello G, Gissler HM, Ruef J, Muller-Hülsbeck S, Jahnke T, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of DURABILITY I study. J Endovasc Ther. 2009;16:261-269.

[12] Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-276.

Lutonix has submitted their original PMA including the data described in this Panel Pack to support their proposed indication of an improvement of luminal diameter in the femoropopliteal arteries.

4 NON-CLINICAL STUDIES

The sponsor conducted *in vitro* performance and characterization studies of the LUTONIX DCB. This included *in vitro* bench testing, chemistry/manufacturing evaluation, biocompatibility, animal studies and toxicity testing.

4.1 In Vitro Bench Testing

Balloon Functional Testing
There are no guidance documents specifically applicable to drug-coated balloons. However, Lutonix elected to follow the relevant sections of the PTCA guidance: "Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters." The purpose of this testing is to ensure that the balloon catheter functions as intended. The following tests were performed on the LUTONIX® 035 Drug Coated Balloon PTA Catheter and results were submitted for review:

- Dimensional and Functional Attributes
- Minimum Balloon Burst Strength
- Balloon Compliance
- Balloon Inflation and Deflation Time
- Balloon Fatigue
- Tensile Strength
- Flexibility and Shaft Kink
- Torque Strength
- Balloon Preparation, Delivery and Retrieval
- Radiopacity

The review team has completed its review of the balloon functional testing and has no outstanding concerns.

Balloon Coating Testing
For drug coated balloons, FDA recommends additional testing of the balloon coating to ensure appropriate coating characteristics. The following balloon coating tests were performed on the LUTONIX® 035 Drug Coated Balloon PTA Catheter and results were submitted for review:

- Coating Integrity
- Drug Coating Uniformity (circumferential and longitudinal)
- Particulate Release
- Particulate Identification
- Coating Physical Properties
- Coating Durability
- Appearance

- Identification
- Assay
- Content Uniformity
- Impurities/ Degradants
- Residual Solvent
- Dissolution

The review team has completed its review of the drug coating testing and has no outstanding concerns related to baseline characterization or stability of the product.

4.2 Chemistry, Manufacturing, and Controls (CMC) Testing

The drug substance, paclitaxel, is purchased from a drug manufacturer. CMC information describing the manufacture and controls of paclitaxel drug substance is incorporated in the LUTONIX® 035 Drug Coated Balloon PTA Catheter PMA by authorized reference to the Drug Master File (DMF). The paclitaxel drug substance meets the quality specifications which were developed based on the US Pharmacopoeia (USP) and European Pharmacopoeia (EP). The CMC information for the drug substance was reviewed and found to be acceptable.

For the finished product, Lutonix has provided the details of the manufacturing process, the quantitative composition of the product, controls for the paclitaxel drug substance used in the manufacture of the LUTONIX DCB, including the analytical test methods and supporting validation data, and stability data. Lutonix has also proposed a finished product specification, including the analytical procedures and supporting validation data. There are no outstanding CMC issues related to these specifications.

4.3 Biocompatibility Testing

Lutonix has identified all material components of the balloon catheter. Lutonix conducted a number of biocompatibility tests to establish the safety profile of the materials used in the LUTONIX DCB on both the uncoated PTA catheter and the drug-coated balloon component. The components were separately tested due to the potential of paclitaxel, a known cytotoxic active pharmaceutical ingredient, to impact the biocompatibility assessment results of the catheter materials and manufacturing processes. Using the same approach, extraction followed by chemical identification of the compounds extracted and a toxicological assessment of these compounds were also performed. The following biocompatibility tests were performed and results were submitted for review:

- Cytotoxicity Study
- Maximization Sensitization
- Intracutaneous
- Systemic Toxicity
- USP Pyrogen Study, Material Mediated
- ASTM Hemolysis
- C3a Complement Activation Assay
- SC5b-9 Complement Activation Assay

- USP Physicochemical Testing
- Fourier Transform Infrared Spectroscopy (FTIR)
- Inductively Coupled Plasma (ICP) Spectroscopy
- Gas Chromatography – Mass Spectrometry (GC/MS)
- Liquid Chromatography/Mass Spectrometry (LC/MS)

There are no outstanding issues regarding biocompatibility.

4.4 Non-clinical In Vivo Animal Studies

Lutonix conducted three GLP animal studies to demonstrate the safety of the clinical dose (acute and chronic) and to evaluate the paclitaxel pharmacokinetics (PK) after angioplasty using the LUTONIX DCB. All animal studies were carried out in a porcine non-atherosclerotic model for durations of up to 6 months. A total of 84 domestic swine underwent experimental procedures across the animal studies.

4.4.1 Nonclinical Safety Summary

Two of the three animal GLP safety studies provided the primary dataset for determining the safety of the clinical dose of paclitaxel that should be incorporated into the DCB, the deliverability of the DCB, and the regional and systemic safety of the DCB in single and overlapped (overdose) usage configurations. Evaluation endpoints included quantitative angiography, clinical safety, histopathology, and device handling. The third GLP study focused on the tissue, organ, and plasma drug PK, but included clinical safety, device evaluation for thrombosis and general observations as part of the overall DCB safety evaluation.
Overall, the animal studies have demonstrated the nonclinical safety of the LUTONIX DCB in an accepted animal model to support the proposed clinical use. The DCB is associated with tolerable low levels of inflammation and injury, predictable evidence of paclitaxel in the development of expected tolerable medial wall thinning with absence of dissection, perforation, or aneurysmal changes to the vascular wall. FDA considered the performance and handling characteristics data as well as the safety and overdose evaluations to be acceptable in advance of initiating human clinical trial. The treated lengths/total available length in the animal studies are representative of the ratios of treated to total vascular length in the humans and provided a reasonable level of assurance that the device was safe enough for clinical investigation.

4.4.2 Nonclinical Pharmacokinetics (Systemic and Arterial Tissue) Summary

The total paclitaxel drug load used for the LUTONIX DCB is higher than previously FDA approved coronary or peripheral drug eluting stents (i.e., generally < 1 mg). Following treatment, systemic levels peaked early (Cmax = 2.88 ng/mL, within 3 minutes), then declined rapidly within 24 hours, and were not detectable at subsequent sampling time points (7, 30, 60, 90 days, etc.). As expected, paclitaxel concentrations were highest in the targeted femoral arterial tissue, compared with other organs, which persisted through Day 180 post treatment. The average arterial tissue concentration at Day 180 was 90 ng/g, a concentration that is higher than generally needed for an anti-proliferative effect (e.g., 1 ng/g). Overall, paclitaxel concentrations observed on Day 180 were approximately 651-, 7.80-, 5.42-, and 302-fold lower

than peak concentrations for artery (C_{max} = 58,900 ng/g) , kidney (C_{max} = 17.7 ng/g), liver (C_{max} = 28.7 ng/g) , and lung (C_{max} = 249 ng/g), respectively. The possible concerns related to the high measured tissue levels of paclitaxel and prolonged retention time were mitigated by the animal and clinical studies, as these data did not reveal any apparent concerns. Please refer to Section 5.2.9 Pharmacokinetic Evaluation for a discussion of the DCB safety profile observed in the clinical studies.

4.5 Toxicology

Toxicology information on paclitaxel was incorporated by reference to the manufacturer's DMF. FDA has reviewed this information and there are no remaining concerns. Based on this information, the labeling proposed by the applicant contains the following contraindication as is consistent with the labeling for paclitaxel: "Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure."

4.6 Sterilization

The LUTONIX® Drug Coated Balloon PTA Catheters are provided sterile. After reviewing the information submitted by the sponsor, the review team has concluded that under the stated exposure conditions, the ethylene oxide cycle will render the LUTONIX DCB systems sterile at a sterility assurance level of 10^{-6}, or the probability of one survivor in one million products sterilized. Ethylene oxide and ethylene chlorohydrin residual analysis was performed to confirm that residual levels are below stated acceptance criteria. Packaging studies were performed to demonstrate that the current packaging configuration will maintain a sterile barrier to support the forthcoming shelf-life claim.

4.7 Manufacturing

FDA has reviewed the manufacturing information. Reviews of the reports from the facility inspections are not yet complete.

5 CLINICAL STUDIES

The clinical trial program primarily includes the pivotal LEVANT 2 trial (randomized patients from both inside and outside the United States) and the earlier LEVANT 1 trial (randomized European). LEVANT 1 was conducted without blinding using an earlier version of the device which had the same drug coating but a 0.018" wire system (instead of a 0.035" system) and used hand balloon folding (instead of an automated folding process). In addition, a Safety Registry Study was initiated for this first-of-a-kind technology in order to further assess device safety with particular interest in assessment of rare unanticipated safety events. The Safety Registry consists of two components, a Continued Access Study, conducted at LEVANT 2 study sites and an additional small safety study conducted at sites that were not included in LEVANT 2 study (see Table 3). Note that the same protocol was used at all Safety Registry sites. Finally, a

Global Superficial Femoral Artery (SFA) Registry has been initiated to assess outcomes in "real world clinical practice."

Table 3: Summary of Clinical Studies

Study	Description	Patient Enrollment/ Follow-up Data	Misc
LEVANT I Randomized Study (NCT00930813)	European Study, Randomized 1:1 (DCB vs. POBA*).	Enrolled: n= 101 patients (49 DCB vs. 52 POBA) Evaluable Follow-up: n=49 pts for safety at 12mths, n= 45 pts for effectiveness at 12mths	Final report completed (2-year follow-up). Used prior model LUTONIX DCB (same drug coating, 0.018" OTW design, hand balloon folding).
LEVANT 2 Pivotal Randomized Study (NCT01412541)	IDE Pivotal Study, Randomized 2:1 (DCB vs. POBA)	Enrolled: n= 543 patients enrolled: 56 roll-in, 476 randomized (316 DCB vs. 160 POBA), 11 standard practice. Evaluable Follow-up (DCB): n= 286 pts for safety at 12mths, n= 264 pts for effectiveness at 12mths	12m report completed. 5-yr follow-up planned (0-2yrs in office visits, 3-5yrs telephonic follow-up). Study is US and Outside US (OUS).
LEVANT 2 Safety Registry (Continued Access; NCT01628159); (**Additional Safety**; NCT01790243)	Collection of additional safety data at LEVANT 2 sites ("Continued Access") and additional sites (Additional Safety)	Enrolled: n= 657 DCB patients Evaluable Follow-up: n=228 pts for safety at 12mths, n= 193 pts for effectiveness at 12mths	Enrollment completed. Follow-up in process. 5-yr follow-up planned (0-2yrs in office visits, 3-5yrs telephonic follow-up). Study is US and OUS
Global SFA Registry (NCT01864278)	Assess clinical use/outcome in a heterogeneous patient population to reflect "real world" use.	Enrolled: n=437 DCB patients Evaluable Follow-up: n=126 pts at 6mths, n= 7 pts at 12mths	Study is OUS only Planned enrollment= 1000 DCB pts. Min of 2 year follow-up planned.

*POBA= Plain Old Balloon Angioplasty

5.1 LEVANT 2 Study Design

Study Name: A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Moxy™ Drug Coated Balloon[13] vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries (LEVANT 2).

[13] Note: The LUTONIX DCB was previously named Moxy™ Drug Coated Balloon

Study Objective: To demonstrate the safety and effectiveness of the LUTONIX DCB for treatment of stenosis or occlusion of the superficial femoral and popliteal arteries.

Study Design: The LEVANT 2 pivotal trial is a prospective, multicenter, single blind, randomized, controlled trial comparing the LUTONIX 035 Drug Coated Balloon PTA Catheter (test group) vs. standard balloon angioplasty (control group) for treatment of *de novo* or non-stented restenotic lesions in native femoropopliteal arteries.

Subjects and Investigational Sites: Enrollment in the LEVANT 2 trial began on July 20, 2011 and was completed on July 10, 2012. Final 12-month follow-up occurred on July 31, 2013. A total of 543 subjects were enrolled at 54 United States (US) and Outside of the United States (OUS) sites, of which:

- 476 patients were randomized 2:1 to LUTONIX DCB (n=316) and PTA (n=160);
- 56 patients were roll-ins; and
- 11 patients were treated per standard practice[14]

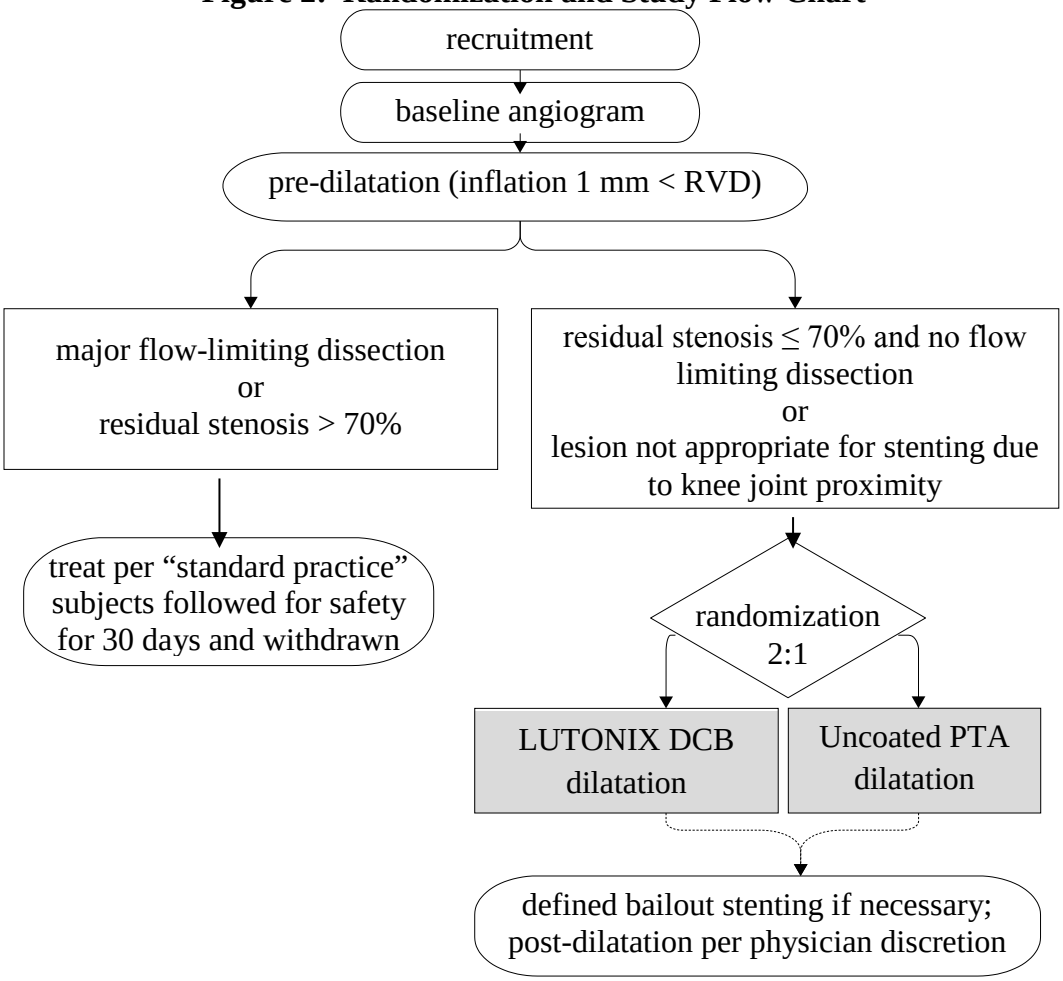
Randomization and Study Flow: A 2:1 randomization ratio (Test: Control) was used after successful pre-dilatation (see Figure 2).

Blinding: The patient, investigator conducting follow-up, Duplex Ultrasound (DUS) evaluators, core lab evaluators and members of the Clinical Events Committee (CEC) were blinded to the subject's treatment. Because the look/feel of the treatment and control devices differed, it was not possible to blind the procedure physician.

Concomitant Medications: All patients were to follow a standard medication regimen regarding the use of aspirin, clopidogrel, or prasugrel. Aspirin was to be continued indefinitely whereas clopidogrel or prasugrel was to be continued for at least one month post-procedure.

[14] Standard practice subjects underwent protocol defined pre-dilatation but did not meet protocol requirements to proceed with randomization, they were not randomized and were followed for 30 days for safety per protocol.

Figure 2: Randomization and Study Flow Chart



Follow-up Schedule: All enrolled subjects in both groups were required to receive follow-up assessments according to the schedule in Table 4. Patients who were predilated and had either a flow-limiting dissection or residual stenosis of greater than 70% were treated per "standard practice" (n=11). These patients were not treated with the LUTONIX DCB; they were followed for 30 days for safety events and then withdrawn.

Table 4: Follow-Up Schedule

Testing Requirements	Screening (pre-consent)	Pre-Procedure	Procedure	Post-Procedure	1 Month[1]	6 Month	12 Month	24 Month	36 Month[1]	48 Month[1]	60 Month[1]
Inclusion/Exclusion Criteria	√	√	√								
Informed Consent		√									
Medical History	√										
Physical Exam		√		√	√	√	√	√			
Medication Compliance		√			√	√	√	√	√	√	√
Resting ABI		√		√	√	√	√	√			
Rutherford Classification		√				√	√	√			
Blood Analysis		√		√	√	√	√				
Six minute Walk Test		√				√	√	√			
WIQ, EQ-5D and SF36-v2 Questionnaires		√				√	√	√			
Angiogram			√								
Adverse Event Monitoring			√	√	√	√	√	√	√	√	√
Duplex Ultrasound (after clinical assessment)				√		√	√	√			
PK Study[2]		√		√	√						

1. Telephone follow-up
2. Subset of patient

Patient Selection Criteria (Selected):

Selected **Inclusion** Criteria

Clinical Criteria
1. Male or non-pregnant female ≥18 years of age
2. Rutherford Clinical Category 2-4

Angiographic Criteria
1. Lesion Length ≤15 cm; Target vessel diameter between ≥4 and ≤6 mm (by operator visual assessment);
2. Lesion starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk;
3. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm);
4. ≥70% stenosis by visual estimate;
5. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by

angiography (treatment of target lesion acceptable after successful treatment (< 30% residual stenosis) of inflow artery lesions);
6. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure);
7. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications.

Selected **Exclusion** Criteria

1. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure;
2. History of MI, thrombolysis or angina within 2 weeks of enrollment;
3. Renal failure or chronic kidney disease;
4. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
5. Anticipated use of Class IIb/IIIa inhibitor prior to randomization;
6. Ipsilateral retrograde access;
7. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
8. Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

Please note that the sponsor revised the patient selection criteria early during the course of the study by expanding the lesion length criterion from "≥ 4 and ≤ 15 cm" to "≤ 15 cm" to allow for treatment of lesions < 4 cm. The sample size was also increased from 336 to 476 to facilitate capturing rare adverse events and adjust for missing imaging data.

Primary Endpoints

Safety – composite of 30-day death and 12-month safety events
Composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index limb-related death.

Effectiveness – 12-month primary patency
Primary Patency is defined as the absence of target lesion restenosis (as adjudicated by blinded core-lab) and freedom from target lesion revascularization (TLR), where

- target lesion restenosis = as adjudicated by blinded DUS core lab (using PSVR≤2.5 and other discerning criteria when necessary), and
- TLR = a repeat revascularization procedure (percutaneous or surgical) of the original target lesion site as adjudicated by the blinded CEC.

Note that the original definition included only a peak-systolic velocity ratio (PSVR) cut-off ≥2.5 (which equates to ~50% stenosis); however, this definition was changed to include total occlusions (PSVR=0) and cases where PSVR alone was insufficient to assess stenosis (e.g., upstream stenosis).

Statistical Analysis

The safety and effectiveness endpoints constituted co-primary endpoints in this study, and a formal statistical hypothesis was prospectively established for each endpoint. The primary analysis was intent-to-treat (ITT), and was performed once all subjects had reached at least 12 months of follow-up. Per-protocol (PP) and as-treated (AT) analyses were also planned to assess the robustness of the study results. In particular, a non-inferiority test as in the primary safety endpoint, ITT analysis attenuates the treatment effect towards the null, i.e., make the treatments appear more similar in effect[15,16,17,18,19,20]. Therefore, PP and AT analyses would provide some reasonable assurance that the absence of rigorous data collection does not skew the results[21].

The ITT composite data set included all randomized subjects according to their assigned treatment. The PP data set included all subjects in the full analysis data set that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified, and the absence of major protocol violations. Specific reasons for exclusion from the PP data set were pre-specified to include: assigned treatment not given, treatment without any pre-dilatation, treatment with geographic miss (as adjudicated by the blinded core lab), and violations of inclusion criteria that if not met for a given subject may obscure the evaluation of effectiveness in that subject. These were to include outflow treatment (not allowed), thrombectomy prior to randomization, and investigator-reported lesion length > 15cm.

Safety – Non-Inferiority Hypothesis

The objective was to test the difference in the proportion of subjects who are free of composite safety events through 12 months post-index procedure between the Test LUTONIX DCB group and the Control PTA group to not exceed 5% worse, tested at a one-sided significance level of 0.025.

$H_0: P_{TEST} - P_{CONTROL} \leq -0.05$ vs. $H_1: P_{TEST} - P_{CONTROL} > -0.05$,

where $p_.$ is the proportion of subjects who did not experienced a composite safety event: all-cause perioperative death within 30 days, or index limb amputation, index limb re-intervention, or index-limb-related death that 1 year post-index procedure.

All-cause perioperative (≤30 day) death, CEC adjudicated index limb amputation (above and

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Simon R: Bayesian design and analysis of active control clinical trials. *Biometrics* **55**: 484-487, 1999.
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[20] Jones B, Jarvis P, Lewis JA, Ebbutt AF: Trials to assess equivalence: the importance of rigorous methods. *Br Med J.* **313**: 36-39, 1996.
[21] Yue, L: Design Issues in Non-Inferiority Medical Device Clinical Trials. Joint Statistical Meeting, Atlanta, GA, 2001.

below the ankle), CEC adjudicated index limb re-intervention, and CEC-adjudicated index-limb-related death are 'safety events'.

Effectiveness – Superiority Hypothesis

The objective was to test that there is no difference in the primary patency rate at 1 year between the Test LUTONIX DCB group and the Control PTA group, tested at a two-sided significance level of 0.05.

H_0: $P_{CONTROL} = P_{TEST}$ vs. H_1: $P_{CONTROL} \neq P_{TEST}$,

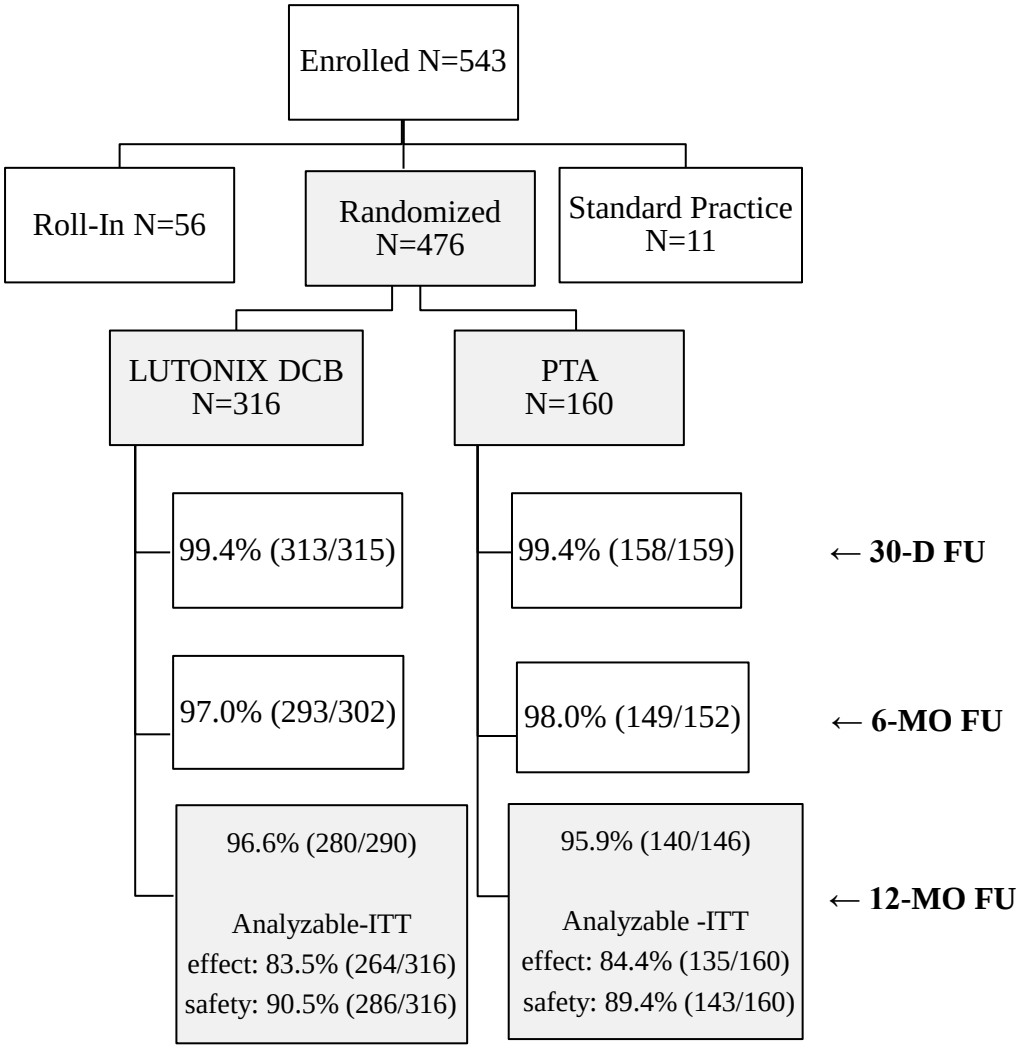
where p is the proportion of subjects with primary patency at 12-month post-index procedure. Core lab adjudicated target lesion restenosis and CEC adjudicated target lesion revascularization (TLR) are 'effectiveness events'.

5.2 LEVANT 2 Study Results

5.2.1 Patient Accountability and Follow-Up

Five hundred forty-three (543) subjects were enrolled in this study, of which 476 subjects were randomized 2:1 to LUTONIX DCB (n=316) and PTA (n=160). There were 56 additional roll-inpatients as well as 11 patients who were enrolled and underwent pre-dilatation, but were not randomized because inclusion criteria were not met after pre-dilatation. These patients were enrolled as "standard practice." The remaining enrolled patients were followed to 12 months with a planned total follow-up to 5 years (see Figure 3: LEVANT 2 Patient Accountability).

Figure 3: LEVANT 2 Patient Accountability



The numerators reflect the number of subjects for whom there is evaluable data and the denominator reflects the number of patients eligible at that time point who are not considered lost-to-follow-up, deceased, or withdrawn. The number of subjects evaluable for the primary endpoints is > 80% of randomized subjects (see Table 5). Since all patients received their intended devices, the AT Population is the same as the ITT population.

Table 5: Evaluable Subjects for Primary Endpoint Analyses (ITT)

Information Source	Test DCB	Control PTA
Analyzable for 12 month Primary Effectiveness Endpoint (Primary Patency)	**83.5% (264/316)**	**84.4% (135/160)**
In-window Clinical Visit with analyzable DUS Completed, without TLR prior to end of 12m window	64.6% (204/316)	58.1% (93/160)
TLR prior to end of 12m window	11.1% (35/316)	15.0% (24/160)

Binary restenosis adjudicated on most recent prior DUS without TLR or evaluable 12m DUS	3.5% (11/316)	6.3% (10/160)
Freedom from TLR and absence of binary restenosis determined by subsequent visit with analyzable DUS	4.4% (14/316)	5.0% (8/160)
Analyzable for 12 month Primary Safety Endpoint	**90.5% (286/316)**	**89.4% (143/160)**
In-window Clinical Visit and/or failed prior to 395 days	81.0% (256/316)	78.8% (126/160)
Freedom from safety events through 395 days demonstrated by subsequent contact	9.5% (30/316)	10.6% (17/160)
Reason Not Evaluable	**Test DCB**	**Control PTA**
Missing for 12 month Primary Efficacy Endpoint (Primary Patency)	**16.5% (52/316)**	**15.6% (25/160)**
Died without prior effectiveness events	1.9% (6/316)	0.6% (1/160)
Withdrew without prior efficacy events	4.1% (13/316)	5.6% (9/160)
Lost-to-follow-up without prior effectiveness events	1.9% (6/316)	0.6% (1/160)
Clinical info through 12m but DUS missing or non-evaluable (without prior effectiveness events)	6.0% (19/316)	5.6% (9/160)
Missed visit at 12m without prior effectiveness events (and no later demonstration of primary patency)	2.5% (8/316)	3.1% (5/160)
Missing for 12 month Primary Safety Endpoint	**9.5% (30/316)**	**10.6% (17/160)**
Died without prior safety events	1.3% (4/316)	1.3% (2/160)
Withdrew without prior safety events	4.1% (13/316)	6.3% (10/160)
Lost-to-follow-up without prior safety events	1.9% (6/316)	0.6% (1/160)
Missed visit at 12m without prior safety events (and no later evidence of success through 12m)	2.2% (7/316)	2.5% (4/160)

5.2.2 Protocol Deviations

There were a large number of protocol deviations reported in the study. A total of 1,293 protocol deviations were reported; among these, there were 823 protocol deviations reported in the test group and 470 in the control group, averaging 2.6 deviations per subject in the LUTONIX DCB arm and 2.9 deviations per subject in the PTA arm. While more protocol deviations were reported in the LUTONIX DCB arm than in the Control PTA arm, the proportion of subjects with at least one reported protocol deviation is lower in the LUTONIX DCB arm than in the PTA arm (71% of subjects for LUTONIX DCB vs. 78% of subjects for PTA). These protocol deviations may produce biased estimate of the treatment effect (see Table 6).

Table 6: Site-Reported Protocol Deviations (ITT)

	Test DCB		Control PTA		All Randomized Subjects	
Protocol Deviations by Type	**Events**	**% (n/N)**	**Events**	**% (n/N)**	**Events**	**% (n/N)**
Bailout stent criteria not met	3	0.9% (3/316)	6	3.8% (6/160)	9	1.9% (9/476)
Data incomplete / not provided	13	4.1% (13/316)	5	3.1% (5/160)	18	3.8% (18/476)
Eligibility criteria not met	8	2.5% (8/316)	11	6.9% (11/160)	19	4.0% (19/476)
Follow-up missed	37	8.2% (26/316)	18	8.8% (14/160)	55	8.4% (40/476)
Follow-up visit done early / late	74	19.0% (60/316)	49	21.3% (34/160)	123	19.7% (94/476)
Geographical miss during procedure	3	09% (3/316)	0	0.0% (0/160)	3	0.6% (3/476)
Medication not given / taken per protocol	90	17.7% (56/316)	49	18.1% (29/160)	139	17.9% (85/476)
Other[1]	39	12.0% (38/316)	27	13.8% (22/160)	66	12.6% (60/476)
Physician became unblinded	1	0.3% (1/316)	0	0.0% (0/160)	1	0.2% (1/476)
Pre-dilatation not done per protocol	4	1.3% (4/316)	2	1.3% (2/160)	6	1.3% (6/476)
Quality of Life questionnaire not done	38	6.0% (19/316)	14	5.0% (8/160)	52	5.7% (27/476)
Required testing incomplete / not provided	163	28.2% (89/316)	89	33.1% (53/160)	252	29.8% (142/476)
Routine blood analysis not performed[2]	273	37.7% (119/316)	137	38.8% (62/160)	410	38.0% (181/476)
SAE submitted to sponsor outside of window	77	19.0% (60/316)	63	25.0% (40/160)	140	21.0% (100/476)
Total	**823**	**70.6% (223/316)**	**470**	**78.1% (125/160)**	**1293**	**73.1% (348/476)**

[1] A listing of "Other" Protocol Deviations can be found in Appendix I of the Clinical Study Report

[2] Note that if even one value of the CBC or CMP was missing, a PD was issued.

5.2.3 Baseline and Procedural Characteristics

Baseline and procedural characteristics were assessed regarding demographics, medical history, clinical characteristics, cardiac medications at baseline, procedural medications, and baseline angiographic data. For the 476 randomized patients that were treated, baseline demographics were similar between the LUTONIX DCB group and the PTA control group (see Table 7). Medical history was also generally well-matched with similar overall incidence of diabetes and stroke in each group; however, there was higher incidence of type I diabetes in the LUTONIX DCB arm and ischemic-type stroke in the Control arm (see Table 8). Clinical characteristics with regard to Rutherford classification and ABI were similar between groups (see Table 9).

Most patients were Rutherford class 3[22] with approximately 8% prevalence of critical limb ischemia in each group. Cardiac medications at baseline as well as procedural medications were comparable between groups. Lesion location, number of lesions treated, and lesion characteristics indicated that the two groups were well-matched (see Table 10). Selected procedural data (see Table 11) suggests that the LUTONIX DCB arm included significant differences compared to the Control group with regard to: (1) a higher number of balloons used (1.37 vs. 1.13, p<0.001); (2) lower inflation pressures (7.8 vs. 8.4 atm, p=0.002) with a trend towards inadequate overstretch; and (3) reduced use of bail-out stenting (2.5% vs. 6.9%, p = 0.022). Because drug delivery occurs only during the first inflation of the DCB and it cannot be repositioned or re-inflated like non-coated PTA catheters, it is expected that a higher number of balloons would be used in the LUTONIX DCB arm. The lower inflation pressures, reduced overstretch and lower bail-out stenting, however, may be a reflection of procedural bias. Although residual diameter stenosis post-procedure was similar in both arms (20.9% DCB vs 21.0% PTA), the overall impact of this potential bias is unclear.

FDA Comment: Baseline demographics, selected medical history, clinical characteristics, concomitant medication use and lesion characteristics were similar between groups. Procedural characteristics varied in that the LUTONIX DCB had lower inflation pressures (with a trend towards inadequate overstretch) and reduced use of bail-out stenting. The Panel should discuss the potential impact of this likely procedural bias.

Table 7: Selected Demographics

Variable	Test DCB	Control PTA	P-value	Pooled
Age (years), Mean ± SD (n) median (min, max)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	69.0 ± 9.0 (160) 69.0 (41.5, 89.4)	0.209	68.2 ± 9.7 (476) 68.4 (41.5, 91.4)
Gender, % (n/N)			0.216	
Female	38.9% (123/316)	33.1% (53/160)		37.0% (176/476)
Male	61.1% (193/316)	66.9% (107/160)		63.0% (300/476)
Ethnicity, % (n/N)			0.741	
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)		8.2% (39/476)
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)		91.6% (436/476)
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)		0.2% (1/476)
Race, % (n/N)			0.160	
Asian	1.3% (4/316)	2.5% (4/160)		1.7% (8/476)
Black or African American	3.8% (12/316)	8.1% (13/160)		5.3% (25/476)
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)		4.2% (20/476)
White	90.8% (287/316)	85.0% (136/160)		88.9% (423/476)
BMI (kg/m^2), Mean ± SD (n) median (min, max)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	28.3 ± 4.8 (160) 27.9 (18.1, 48.5)	0.221	28.7 ± 5.2 (476) 28.1 (15.8, 52.7)

[22] See Appendix 2 for Rutherford Classifications Definitions

Table 8: Selected Medical History

Variable	Test DCB	Control PTA	P-value	Pooled
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360	33.4% (159/476)
Smoking, % (n/N)			0.548	
Current smoker	35.1% (111/316)	33.8% (54/160)		34.7% (165/476)
Never smoked	20.9% (66/316)	17.5% (28/160)		19.7% (94/476)
Previously smoked	44.0% (139/316)	48.8% (78/160)		45.6% (217/476)
Dyslipidemia/Hypercholesterolemia, % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286	88.4% (421/476)
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758	42.9% (204/476)
Type			0.034	
Type I	9.5% (13/137)	1.5% (1/67)		6.9% (14/204)
Type II	90.5% (124/137)	98.5% (66/67)		93.1% (190/204)
Insulin Dependency	40.9% (56/137)	40.3% (27/67)	0.937	40.7% (83/204)
Hypertension, % (n/N)	89.2% (282/316)	87.5% (140/160)	0.572	88.7% (422/476)
Renal Failure, % (n/N)	3.5% (11/316)	4.4% (7/160)	0.629	3.8% (18/476)
Congestive Heart Failure, % (n/N)	5.7% (18/316)	3.1% (5/160)	0.217	4.8% (23/476)
Previous CAD, % (n/N)	49.7% (157/316)	48.1% (77/160)	0.748	49.2% (234/476)
Previous MI, % (n/N)	19.9% (63/316)	17.5% (28/160)	0.523	19.1% (91/476)
Chronic Angina, % (n/N)	4.7% (15/316)	5.0% (8/160)	0.903	4.8% (23/476)
History of Coronary Revascularization, % (n/N)	41.8% (132/316)	38.8% (62/160)	0.526	40.8% (194/476)
Type of Coronary Revascularization			0.429	
CABG	45.2% (47/104)	52.1% (25/48)		47.4% (72/152)
PCI	54.8% (57/104)	47.9% (23/48)		52.6% (80/152)
Previous Cerebrovascular Event, % (n/N)	11.4% (36/316)	11.3% (18/160)	0.963	11.3% (54/476)
Ischemic	75.0% (27/36)	100.0% (18/18)	0.020	83.3% (45/54)
Hemorrhagic	5.6% (2/36)	0.0% (0/18)	0.308	3.7% (2/54)
Previous Target Limb Intervention, % (n/N)	23.4% (74/316)	17.5% (28/160)	0.137	21.4% (102/476)
Target Vessel Type			0.292	
DeNovo Target Vessel	83.9% (265/316)	87.5% (140/160)		85.1% (405/476)
Restenosed Target Vessel	16.1% (51/316)	12.5% (20/160)		14.9% (71/476)

Table 9: Clinical Characteristics

Variable	Test DCB	Control PTA	P-value	Pooled
Rutherford Grade, % (n/N)			0.521	
2	29.4% (93/316)	34.4% (55/160)		31.1% (148/476)
3	62.7% (198/316)	57.5% (92/160)		60.9% (290/476)
4	7.9% (25/316)	8.1% (13/160)		8.0% (38/476)
ABI of Target Limb[1], Mean ± SD (n) median (min, max)	0.74 ± 0.20 (306) 0.73 (0.00, 1.38)	0.73 ± 0.18 (156) 0.73 (0.00, 1.17)	0.467	0.74 ± 0.20 (462) 0.73 (0.00, 1.38)
ABI of Contralateral Limb, Mean ± SD (n) median (min, max)	0.87 ± 0.23 (301) 0.92 (0.00, 1.34)	0.87 ± 0.20 (152) 0.89 (0.00, 1.30)	0.783	0.87 ± 0.22 (453) 0.91 (0.00, 1.34)

1. Pressures > 1.4 were excluded from this analysis (n = 3 for LUTONIX DCB, n = 1 for PTA)

Table 10: Selected Baseline Angiographic Characteristics

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Number of Lesions Treated			0.400	
1	98.1% (310/316)	96.9% (155/160)		97.7% (465/476)
2	1.9% (6/316)	3.1% (5/160)		2.3% (11/476)
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	63.2 ± 40.4 (160) 51.8 (7.5, 173.7)	0.900	62.8 ± 41.0 (475) 51.6 (5.7, 196.7)
Treated Length (mm), Mean ± SD(n) median (min, max)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	107.9 ± 49.4 (160) 103.4 (23.3, 307.7)	0.988	107.9 ± 47.8 (476) 104.9 (23.3, 307.7)
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	80.9 ± 14.9 (160) 82.0 (45.0, 100.0)	0.776	80.6 ± 14.8 (476) 81.0 (40.0, 100.0)
Lesion Class TASC II, % (n/N)			0.398	
A	76.3% (241/316)	75.6% (121/160)		76.1% (362/476)
B	21.5% (68/316)	23.8% (38/160)		22.3% (106/476)
C	2.2% (7/316)	0.6% (1/160)		1.7% (8/476)
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826	58.8% (280/476)
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419	97% (46/476)
Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741	21.0% (100/476)
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (160) 2.0 (0.0, 3.0)	0.148	2.0 ± 1.0 (476) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539	
0	9.5% (30/316)	13.1% (21/160)		10.7% (51/476)
1	15.2% (48/316)	16.9% (27/160)		15.8% (75/476)
2	35.4% (112/316)	35.0% (56/160)		35.3% (168/476)
3	39.9% (126/316)	35.0% (56/160)		38.2% (182/476)
Most Distal Lesion Location, %(n/N)			0.495	
Proximal SFA	9.2% (29/316)	8.1% (13/160)		8.8% (42/476)
Mid SFA	51.3% (162/316)	45.6% (73/160)		49.4% (235/476)
Distal SFA	29.7% (94/316)	38.8% (62/160)		32.8% (156/476)
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)		4.6% (22/476)
Mid Popliteal	4.1% (13/316)	2.5% (4/160)		3.6% (17/476)
Distal Popliteal	0.9% (3/316)	0.6% (1/160)		0.8% (4/476)
Most Distal Lesion Location Rank[3], Mean ± SD (n); median (min, max)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.49 ± 0.85 (160) 2.00 (1.00, 6.00)	0.721	2.47 ± 0.91 (476)) (1.00, 6.00)

1. All values per angiographic core lab except where indicated
2. T-tests for means and X2-tests for proportions
3. Lesion locations are ranked 1-6 from least to most distal, in the order displayed.

Table 11: Procedural Data

Variable	Test DCB	Control PTA	P-value[2]	Pooled
Contralateral Access, % (n/N)	73.4% (232/316)	73.8% (118/160)	0.938	73.5% (350/476)
Inflow Tract Stenosis Treated, % (n/N)	0.9% (3/316)	1.9% (3/160)	0.392	1.3% (6/476)
Predilation				
Predilation Performed (All Lesions), % (n/N)	100.0% (316/316)	100.0% (160/160)		100.0% (476/476)
Predilation Overstretch (Inflated Diameter/RVD, core lab), Mean ± SD (n) median (min, max)	0.8 ± 0.2 (283) 0.8 (0.3, 1.3)	0.8 ± 0.2 (138) 0.8 (0.5, 1.3)	0.234	0.8 ± 0.2 (421) 0.8 (0.3, 1.3)
Maximum %DS Post Predilation (Core Lab), Mean ± SD (n) median (min, max)	40.8 ± 12.9 (312) 41.0 (2.0, 88.0)	41.9 ± 13.5 (156) 41.0 (12.0, 80.0)	0.375	41.1 ± 13.1 (468) 41.0 (2.0, 88.0)
As-randomized study device treatment				
Total Number of Treatment Balloons, Mean ± SD (n) median (min, max)	1.37 ± 0.50 (316) 1.00 (1.00, 3.00)	1.13 ± 0.35 (160) 1.00 (1.00, 3.00)	<0.001	1.29 ± 0.47 (476) 1.00 (1.00, 3.00)
Total Number of Treatment Balloons (Categorical), % (n/N)			<0.001	
1	63.9% (202/316)	88.1% (141/160)		72.1% (343/476)
2	35.4% (112/316)	11.3% (18/160)		27.3% (130/476)
3	0.6% (2/316)	0.6% (1/160)		0.6% (3/476)
Total Paclitaxel on Balloons Used per Subject (mg), Mean ± SD (n) median (min, max)	3.5 ± 1.8 (316) 3.1 (1.0, 11.3)	N/A		3.5 ± 1.8 (316) 3.1 (1.0, 11.3)
Transit Time per Balloon (seconds), Mean ± SD (n) median (min, max)	35.2 ± 27.2 (432) 30.0 (3.0, 179.0)	N/A		35.2 ± 27.2 (432) 30.0 (3.0, 179.0)
Inflation Time per Balloon (seconds), Mean ± SD (n) median (min, max)	151.2 ± 78.1 (432) 120.0 (30.0, 480.0)	173.6 ± 109.6 (180) 135.0 (10.0, 630.0)	0.004	157.8 ± 89.0 (612) 120.0 (10.0, 630.0)
Maximum Pressure of Study Balloons (per balloon), Mean ± SD (n) median (min, max)	7.8 ± 2.0 (432) 8.0 (4.0, 14.0)	8.4 ± 2.6 (180) 8.0 (3.0, 14.0)	0.002	8.0 ± 2.2 (612) 8.0 (3.0, 14.0)
Treatment Overstretch (inflated diameter/RVD), Mean ± SD (n) median (min, max)	0.9 ± 0.2 (294) 0.9 (0.5, 1.6)	1.0 ± 0.2 (145) 1.0 (0.6, 1.7)	0.098	0.9 ± 0.2 (439) 0.9 (0.5, 1.7)
Dissection post-study treatment (Core Lab), % (n/N)	63.4% (199/314)	71.7% (114/159)	0.071	66.2% (313/473)
Dissection Grade post-study treatment (Core Lab)			0.034	
Grade A	37.6% (118/314)	38.4% (61/159)		37.8% (179/473)
Grade B	23.2% (73/314)	25.8% (41/159)		24.1% (114/473)
Grade C	2.5% (8/314)	7.5% (12/159)		4.2% (20/473)
Dissection post-study treatment (Site Reported), % (n/N)	39.6% (125/316)	38.8% (62/160)	0.865	39.3% (187/476)

Dissection Treated (Site Reported)	36.0% (45/125)	37.1% (23/62)	0.883	36.4% (68/187)
Dissection Treatment - PTA (Site Reported)	97.8% (44/45)	65.2% (15/23)	<0.001	86.8% (59/68)
Dissection Treatment - Stent (Site Reported)	8.9% (4/45)	39.1% (9/23)	0.003	19.1% (13/68)
Maximum %DS Post study treatment (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	23.4 ± 12.3 (316) 24.0 (0.0, 100.0)	23.8 ± 12.3 (158) 24.0 (0.0, 59.0)	0.703	23.5 ± 12.3 (474) 24.0 (0.0, 100.0)
Additional Treatments (Any Lesion)				
PTA, % (n/N)	21.5% (68/316)	20.0% (32/160)	0.701	21.0% (100/476)
Stent, % (n/N)	2.5% (8/316)	6.9% (11/160)	0.022	4.0% (19/476)
Final Procedural Outcome				
Maximum %DS Post Procedure (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	20.9 ± 9.8 (316) 22.0 (0.0, 47.0)	21.0 ± 10.2 (159) 22.0 (0.0, 47.0)	0.914	20.9 ± 9.9 (475) 22.0 (0.0, 47.0)
Minimum Lumen Diameter (MLD) Post procedure (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	3.8 ± 0.7 (316) 3.8 (2.4, 6.0)	3.9 ± 0.7 (159) 3.8 (2.4, 6.4)	0.365	3.8 ± 0.7 (475) 3.8 (2.4, 6.4)
Final Procedural Dissection (Core Lab), % (n/N)	62.9% (198/315)	64.2% (102/159)	0.783	63.3% (300/474)
Final Procedural Dissection Grade (Core Lab)			0.174	
Grade A	37.5% (118/315)	37.1% (59/159)		37.3% (177/474)
Grade B	23.5% (74/315)	21.4% (34/159)		22.8% (108/474)
Grade C	1.9% (6/315)	5.7% (9/159)		3.2% (15/474)
Procedure Duration (Minutes), Mean ± SD (n) median (min, max)	57.6 ± 29.8 (316) 54.0 (14.0, 268.0)	56.6 ± 29.2 (160) 52.0 (8.0, 161.0)	0.741	57.3 ± 29.6 (476) 53.5 (8.0, 268.0)
Geographic Miss[1] (Any Lesion), % (n/N)	7.6% (24/316)	21.9% (35/160)	<0.001	12.4% (59/476)
Procedural Embolism, % (n/N)	0.6% (2/316)	1.9% (3/160)	0.209	1.1% (5/476)
Procedural Success (Core Lab, All Lesions), % (n/N)	88.9% (281/316)	86.8% (138/159)	0.497	88.2% (419/475)

1. Core lab adjudication if known, otherwise site adjudication.
2. T-tests for means and X2-tests for proportions.

5.2.4 Primary Safety Results

The primary analysis of the safety primary endpoint was a comparison of the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index limb-related death in the ITT population (see Table 12 and Table 13).

Within the 12-month evaluation period, there were no perioperative or index-limb related deaths. Only one amputation was observed which occurred in the LUTONIX DCB arm. The safety endpoint was driven by Target Limb Revascularization at 12 months with 15.4% (44/285) in the LUTONIX DCB group and 21.0% (30/143) in the Control group. Overall Freedom from Primary Safety Event was 83.9% (240/286) for the LUTONIX DCB arm and 79.0% (113/143) for the Control arm. The difference was 4.9% with a two-sided 95% confidence interval of (-2.6%, 12.3%), excluding the non-inferiority margin of -5%. Based on the ITT populations, the non-inferiority objective of the LUTONIX DCB compared to Control PTA was met (p=0.005).

In addition to the primary ITT analysis, a pre-specified PP analysis was performed. The PP dataset excluded patients if treatment did not follow protocol defined procedures or inclusion criteria were violated. Specific reasons for exclusion from the PP dataset were prespecified and included: assigned treatment not given, no predilatation, geographic miss, and inclusion criteria not met. The primary reason for exclusion from the PP analysis was geographic miss, as adjudicated by the core lab, where the entire predilated injury segment was not treated with the assigned device. Geographic miss resulted in exclusion of 7.6% (24/316) of LUTONIX DCB patients and 21.9% (35/160) of Control patients in the PP analysis. The pre-specified PP safety analysis resulted in safety success rates of 83.7% (221/264) and 83.0% (88/106) for the LUTONIX DCB and Control groups, respectively. The difference was 0.7% with a two sided 95% confidence interval of (-7.3%,8.7%), which includes the non-inferiority margin of -5%. Although the rates of the primary safety endpoint were similar between the two treatment groups, the difference was not large enough to meet the non-inferiority objective of the LUTONIX DCB compared to the Control PTA arm (p=0.08).

Table 12: Primary Safety Endpoint

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
ITT: Freedom from Primary Safety Event[1]	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-2.6, 12.3]	0.005
PP: Freedom from Primary Safety Event[1]	83.7% (221/264) [79.3, 88.2]	83.0% (88/106) [75.9, 90.2]	0.7% [-7.3, 8.7]	0.08

1. Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
2. P-value (non-inferiority) and CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. Margin of non-inferiority 5%.

Table 13: Types of Primary Safety Events (ITT Population)

Safety Event *(subject may have more than one event)*	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference[1] % [95% CI]**
Perioperative (≤30) Death	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%
Index Limb Related Death at 12 Months	0.0% (0/285) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]	0.0%
Amputation at 12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]	0.3% [-0.3, 1.0]
Target Limb Revascularization 12 months	15.4% (44/285) [11.2, 19.6]	21.0% (30/143) [14.3, 27.7]	-5.5% [-14.0, 1.7]

1. Nominal CI for difference based on a Farrington-Manning method are provided but were not pre-specified for hypothesis testing and are not adjusted for multiplicity. CI for groups are asymptotic.

An additional analysis for the primary safety endpoint was performed using the Kaplan-Meier method. The Kaplan-Meier curve and estimates for freedom from the safety primary endpoint based on the ITT population are included in Figure 4 and Table 14, respectively.

Figure 4: Kaplan-Meier Graph of Primary Safety Endpoint (ITT Population)

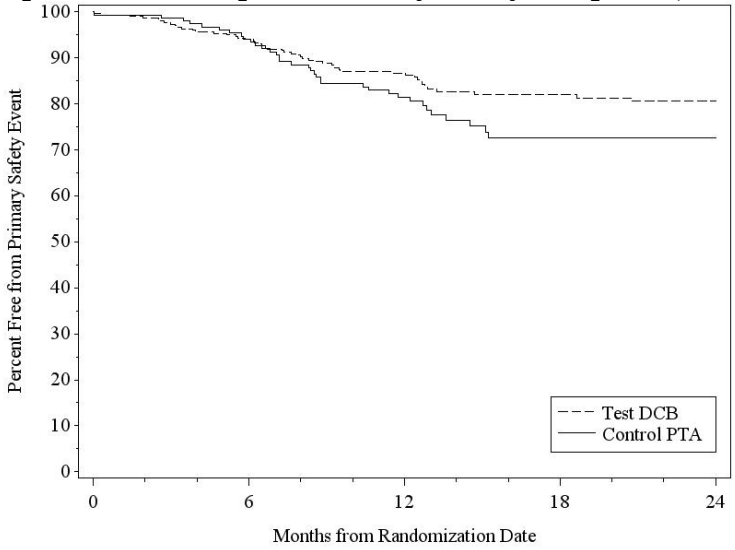


Table 14: Freedom from Composite Safety Events by Kaplan-Meier (ITT Population)

	Test DCB				Control PTA			
Time[1]	**Survival %[95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**	**Survival %[95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**
30 days	99.4%	2	9	305	99.4%	1	5	154
183 days	94.0%	18	21	277	94.1%	9	13	138
365 days	86.7% [82.3, 90.1]	39	66	211	81.5% [74.1, 86.9]	27	35	98
730 days	80.6%	50	226	40	72.6%	35	108	17

1. Survival is the absence of the composite endpoint of failure from all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
2. Nominal confidence intervals and log rank p values (for test of superiority) provided although not prespecified for hypothesis testing and not adjusted for multiplicity.

To address the impact of missing data on the robustness of the study conclusion, tipping point analyses were also performed. Figure 4 and Figure 5 present all possible scenarios (combination) of missing primary safety endpoints between the two groups. The x-axis represents the missing primary safety endpoints for the Control PTA as successes, and the y-axis represents the missing endpoints for the LUTONIX DCB as successes. The yellow region is the scenario where the primary safety objective would be met (the LUTONIX DCB is non-inferior to the Control PTA), whereas the red region is the scenario where the objective would fail (the LUTONIX DCB is not non-inferior to the Control PTA). Figure 5 is for the ITT analysis, and Figure 6 is for the PP analysis. If we assume that the data are missing at random and the expected rate of each arm in the missing cohort is the same as the observed rate in the entire cohort (green dot with its observed 95% confidence band around it),, then the observed point falls in the yellow region for the ITT population, which suggests that there is a good chance that the test LUTONIX DCB is non-inferior to the control standard PTA (assuming missing completely at random). However, the observed point falls in the red region for the PP

population, which suggests that it is unlikely that the test LUTONIX DCB is non-inferior to the control standard PTA (assuming missing completely at random).

Figure 5: Tipping Point Analysis of Primary Safety Endpoint (ITT Population)

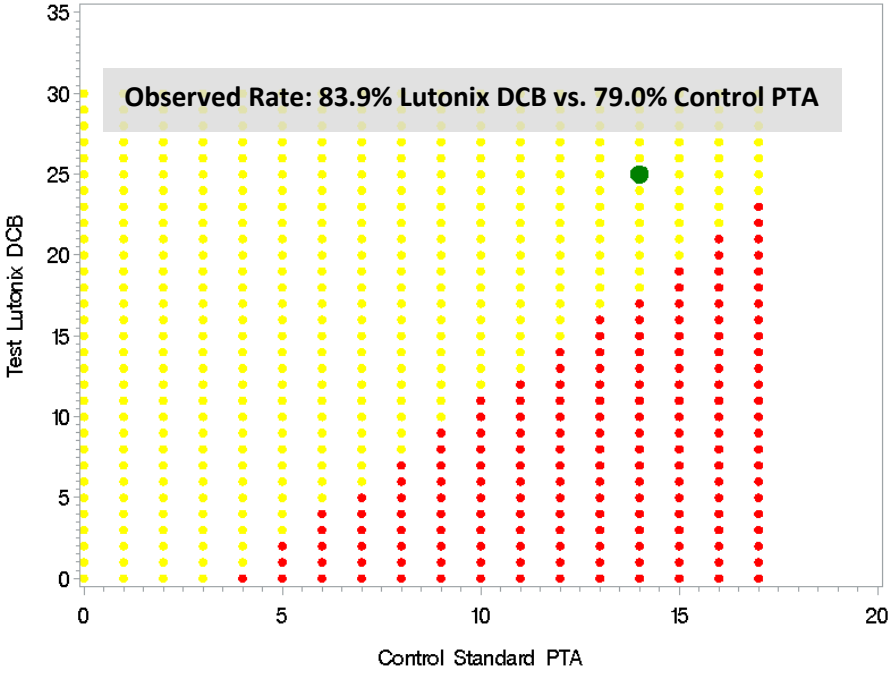
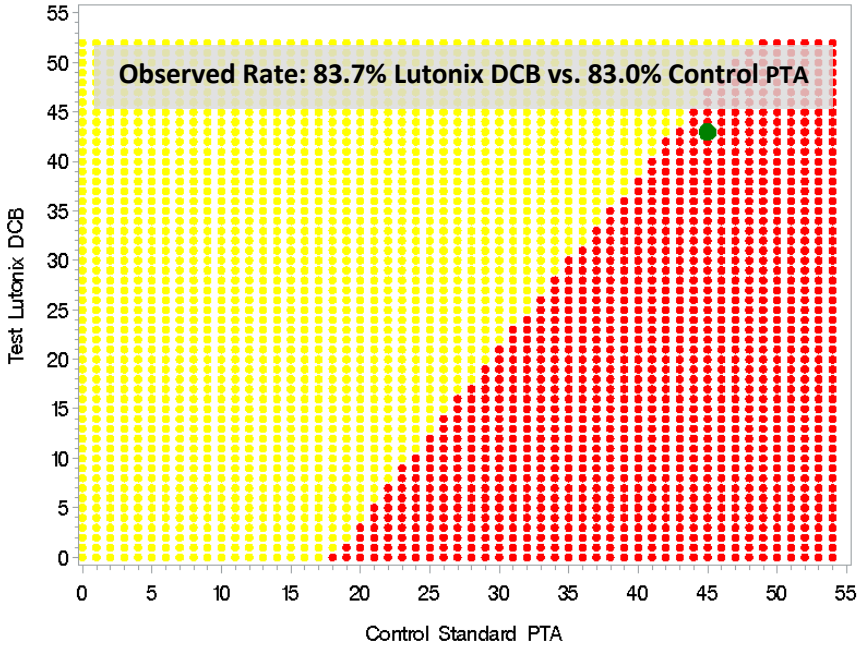


Figure 6: Tipping Point Analysis of Primary Safety Endpoint (PP Population)



Missing data rate in the ITT analysis population was comparable between the treatment groups (17/160=10.6% for the Control PTA vs. 30/316=9.5% for the LUTONIX DCB). There were

substantially more subjects in the Control PTA arm than the LUTONIX DCB arm who were excluded from the PP analysis (54/160=33.8% vs. 52/316=16.5%, respectively). This implies that it is possible that the missing at random assumption in the tipping point analysis may not hold, and there may be bias associated with the results.

FDA Comment: The non-inferiority criterion for the primary safety endpoint was met for the ITT population and the result is relatively robust to missing data. However, the non-inferiority criterion was not met for the primary safety endpoint for the PP population. The sponsor reported that this finding was primarily driven by the disproportionate exclusion of endpoint events in the Control arm because of "geographic miss," (i.e., not treating the entire predilated injury segment). The panel will be asked to comment on the robustness of the primary safety endpoint conclusion.

5.2.5 Primary Effectiveness Results

The primary analysis of the primary effectiveness endpoint was a comparison of the Primary Patency, defined as the absence of target lesion restenosis (as adjudicated by blinded core-lab) and freedom from TLR (see Table 15 and Table 16). Within the 12-month evaluation period, there were 92 and 62 primary effectiveness endpoint events in the LUTONIX DCB and Control arms, respectively. The 12-month Primary Patency rate was 65.2% (172/264) in the LUTONIX DCB arm compared to 52.6% (71/135) in the Control arm and the difference is statistically significant with (p= 0.02); therefore, the primary effectiveness endpoint was met for the ITT analysis. For both study arms, primary patency events were attributed to TLR in approximately 1/3 of patients and attributed to restenosis by DUS in approximately 2/3 of patients.

Table 15: Primary Effectiveness Endpoint

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
ITT: Primary Patency[1]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
PP: Primary Patency[1]	65.3% (160/245) [59.3, 71.3]	56.0% (56/100) [46.3,65.7]	9.3% [-2.1, 20.7]	0.11

1. Primary Patency is defined freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
2. Based on asymptotic likelihood ratio test. CIs for groups and difference are asymptotic.

Table 16: Types of Primary Effectiveness Events (ITT Population)

Effectiveness Event	Test DCB %(n/N Failures) [95% CI]	Control PTA %(n/N Failures) [95% CI]	Difference % [95% CI]
TLR	38.0% (35/92) [26.1, 45.7]	37.5% (24/62) [25.6, 49.4]	0.5% [-14.9, 16.0]
Adjudicated Restenosis without TLR	62.0% (57/92) [52.0, 71.9]	62.5% (40/64) [50.6, 74.4]	-0.5% [-16.0, 14.9]

In addition to the primary ITT analysis, the sponsor performed a pre-specified PP analysis to further evaluate the robustness of the ITT conclusions. This resulted in effectiveness success rates of 65.3% (160/245) and 56% (56/100) for the LUTONIX DCB and Control groups, respectively. The difference was 9.3% with a two-sided 95% confidence interval of -2.1 and 20.7 and a corresponding p-value of 0.11. Similar to the primary safety analysis, the primary effectiveness analysis resulted in statistically significant differences between groups for the ITT analysis, but the PP did not show a difference between the LUTONIX DCB and the Control arm. As an additional analysis, The Kaplan-Meier curve and estimates for freedom from the effectiveness primary endpoint based on the ITT population are included in Figure 7 and Table 17, respectively.

Figure 7: Kaplan-Meier Graph of Primary Effectiveness Endpoint (ITT Population)

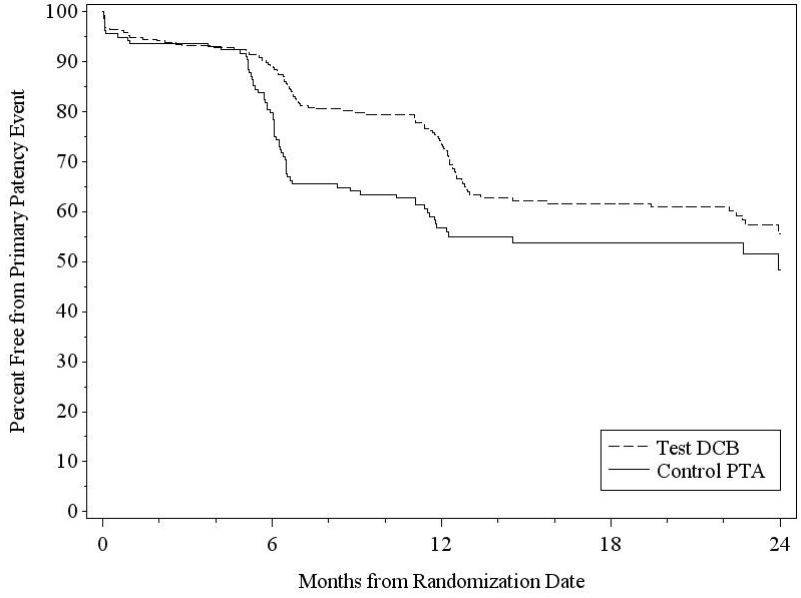


Table 17: Freedom from Composite Effectiveness Events by Kaplan-Meier (ITT Analysis)

	Test DCB				Control PTA			
Time[1]	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**	**Survival % [95% CI]**	**Subjects with Event**	**Censored Subjects**	**Subjects at Risk**
30 days	94.9%	16	9	291	93.7%	10	4	146
183 days	88.8%	34	21	261	78.5%	33	11	116
365 days	73.5% [68.0, 78.2]	77	60	179	56.8% [48.3, 64.4]	64	27	69
730 days	53.7%	108	182	26	48.4%	69	77	14

1. Primary Patency is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR).
2. Nominal confidence intervals and log rank p-values provided although not prespecified for hypothesis testing and not adjusted for multiplicity.

FDA Comment: Based on the interim 24 month results, compared to 365 days, there is a diminished treatment effect noted at 730 days (24 months) of follow-up. Noting the minimal sample size out to 24 months, the Panel will be asked to discuss this issue.

In addition, a tipping point analysis was performed to assess the impact of missing data on the primary effectiveness endpoint conclusion. The following figures present all possible scenarios (combination) of missing primary effectiveness endpoints between the two groups (see Figure 8 and Figure 9). The x-axis represents the missing primary effectiveness endpoints for the Control PTA as successes, and y-axis represents the missing endpoints for the LUTONIX DCB as successes. The tipping point analysis results were inconsistent between the ITT and the PP analyses: the observed rates fall in the yellow region for the ITT (the objective would be met) population but the observed rates fall in the red region for the PP population (the objective would not be met).

Figure 8: Tipping Point Analysis of Primary Effectiveness Endpoint (ITT Population)

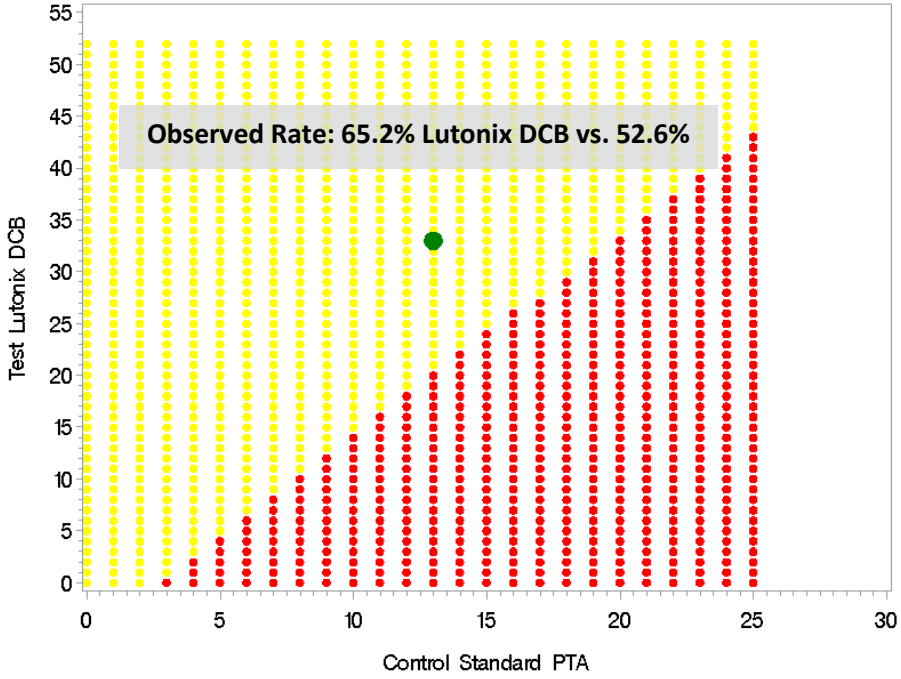
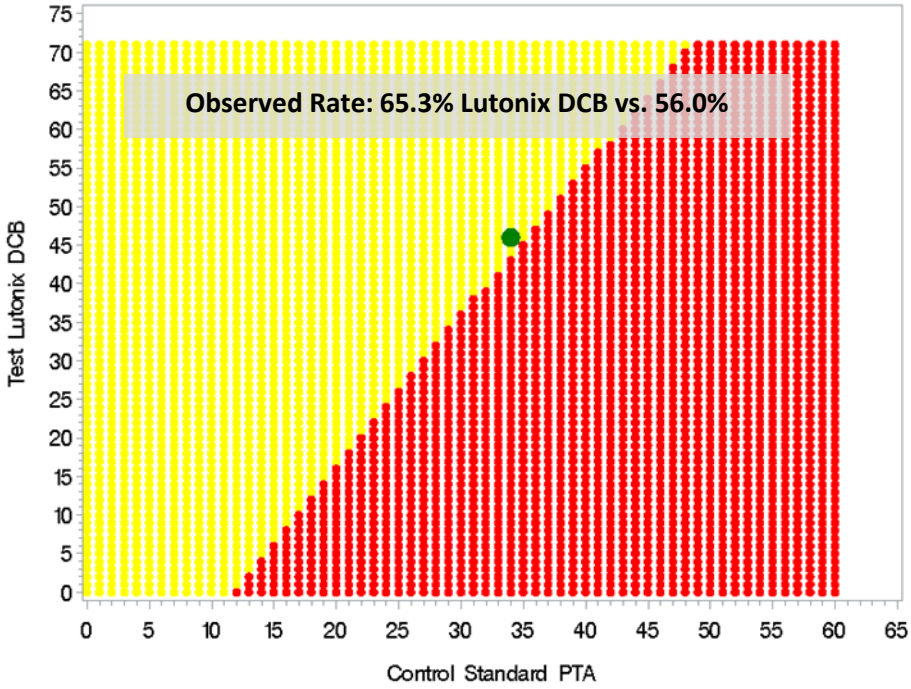


Figure 9: Tipping Point Analysis of Primary Effectiveness Endpoint (PP Population)



Missing data rate in the ITT analysis population was comparable between the treatment groups (25/160=15.6% for the Control PTA vs. 52/316=16.5% for the LUTONIX DCB). There were substantially more subjects in the Control PTA arm than the LUTONIX DCB arm who were excluded from the PP analysis (60/160=37.5% vs. 71/316=22.5%, respectively). This implies that it is possible that the missing at random assumption in the tipping point analysis may not hold, and there may be bias associated with the results.

FDA Comment: The primary patency rate was higher for the LUTONIX DCB arm (65.2%; 172/264) compared to the Control arm (52.6%; 71/135) with a p-value of 0.02 in the ITT population demonstrating statistical superiority of the LUTONIX DCB compared to PTA alone. However, a statistically significant difference was not detected in the PP population in the primary patency rate between the two arms with a p-value of 0.11. With imbalance of protocol deviations between the two treatment groups (22.5%=71/316 for LUTONIX DCB vs. 37.5%=60/160 for the Control PTA) in mind, the Panel will be asked to comment on the clinical significance of the differences in study outcomes between the ITT and the PP analyses.

In addition, to primary patency assessments using a PSVR ≥ 2.5 threshold, primary patency was reassessed using alternative thresholds of 2.0 and 3.0. Statistical significance for primary patency is maintained at the 3.0 threshold (p=0.022); however, there was not a significant difference at the 2.0 threshold (p=0.130).

5.2.6 Secondary Endpoint Analyses

The sponsor prespecified nine secondary endpoints with hypotheses that were to be tested using a hierarchical procedure. That is, each hypothesis was to be tested in a pre-specified order using a

hierarchical testing procedure such that as soon as a null hypothesis is *not* rejected, no further hypotheses would be tested. This method preserves the 0.05 Type I error rate. The first hypothesis tested, total TLR at 12 months, failed to show that the LUTONIX DCB was superior to PTA (p=0.208); therefore, additional secondary endpoints were not tested. For information purposes, the results from the first three pre-specified secondary endpoints planned for hierarchical analysis at the 12-month follow-up (i.e., TLR at 12 months, Target Vessel Revascularization (TVR) at 12 months, composite safety at 12 months) are included in Table 18.

Table 18: Pre-Specified Secondary Endpoints

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[1]
Total TLR at 12 Months	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]	-4.5% [-11.7, 2.7]	0.208
Total TVR at 12 Months	13.3% (38/285)	18.2% (26/143)	-4.8%	-----
Composite Safety Events[2] at 12 Months	16.1% (46/286)	21.0% (30/143)	-4.9%	-----

1. Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.
2. The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death at 12 months.

FDA Comment: The sponsor planned hypothesis testing for nine secondary endpoints in a hierarchical fashion. Because the first analysis in the hierarchy was not significant (i.e., TLR at 12 months; p=0.208), the remainder were not tested. Although a statistically significant difference with respect to primary patency was observed in the ITT analysis, there was no difference in TLR at 12 months between the LUTONIX DCB and PTA. The Panel will be asked to comment on the clinical significance of this issue.

Several additional non-powered endpoints were also assessed and reported with descriptive statistics. Results were generally similar between groups and endpoints included, but were not limited to, assessment of primary patency and secondary patency related to PSVR threshold, TLR (total and clinically driven) and multiple additional standardized assessments including changes from baseline in Rutherford classification, ABI, walking assessments (i.e., Walking Impairment Questionnaire Score, Six-Minute Walk test) and overall health assessments (i.e., EQ-5D, SF-36v2). Finally, various secondary safety endpoints were evaluated regarding specific adverse events at various timepoints and, generally, no substantial differences were noted between groups.

For informational purposes, Appendix 1 shows the results from all pre-specified secondary endpoints.

5.2.7 Subgroup Analyses

Potential difference in treatment effect between the test treatment and the control treatment was

assessed across various subgroups: bail-out stenting status, VIVA OPC entry criteria[23], chronic total occlusion status, lesion length in quartile, lesion length ≥ 12 cm vs. < 12 cm, lesion length ≥ 14 cm vs. < 14 cm, most distal lesion location (proximal SFA, mid SFA, distal SFA, proximal popliteal, mid popliteal, and distal popliteal), lesion location (popliteal, SFA, and SFA and popliteal), number of balloons (multiple vs. single), gender, and geography (OUS vs. US). All interactions were tested at a significance level of 0.15 using the ITT population.

Significant interactions were detected between geography (US vs. OUS) and treatment groups for the primary safety (p=0.02) and the primary effectiveness endpoints (p=0.12). The LUTONIX DCB performed better in the OUS than the US in terms of the freedom from primary safety event rate and the primary patency rate at 1 year (see Table 19). The difference in freedom from primary safety event between DCB and PTA in the OUS was 17.0% in favor of the LUTONIX DCB, but in the US was -2.2% in favor of the Control PTA. The difference in the primary patency rate between the LUTONIX DCB and the Control PTA was reduced from 23.1% in the OUS to 6.4% in the US. These results showed that the OUS data and US data cannot be pooled. It is not clear, therefore, if the OUS data is applicable the US population.

Table 19: Primary Endpoint Rates at 1 Year by Geography (ITT Population)

		Test	**Control**	Difference[3]	p-value
Freedom from Primary Safety Event[1]	OUS	88.7% (94/106)	71.7% (38/53)	17.0%	0.02
	US	81.1% (146/180)	83.3% (75/90)	-2.2%	
Primary Patency[2]	OUS	69.1% (67/97)	46.0% (23/50)	23.1%	0.12
	US	62.9% (105/167)	56.5% (48/85)	6.4%	

1. Composite of freedom from safety events, including all-cause perioperative (≤30 day) death, index limb imputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
2. Primary Patency is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR).
3. CI for difference in safety based on a Farrington-Manning method. CI for difference in primary patency based on asymptotic likelihood ratio test. Confidence intervals are provided without adjustment for multiplicity; hypothesis testing of geographic subsets was not prespecified.

There was no significant interaction detected between gender and the treatment group for the primary safety endpoint (p=0.30); however, a significant qualitative interaction was shown for the primary effectiveness endpoint (p=0.01). After adjusting for the quantitative interaction between region and the treatment group, there was still a significant interaction between gender and the treatment group (p=0.01). Furthermore, there were statistically significant interactions between geography, gender, and the treatment groups for both the primary safety endpoint (p=0.001) and the primary effectiveness endpoint (p=0.07). Table 20 depicts the primary safety event and primary patency rate at 1 year by geography and gender. In 'US Males,' the LUTONIX DCB arm had better outcomes than the control arm for both the primary safety and effectiveness endpoints. However, in 'US females,' the LUTONIX DCB arm had no better outcomes than the control arm for both the primary safety and effectiveness endpoints.

[23] VIVA OPC entry criteria= Lesion(s) terminates in SFA or proximal popliteal, lesion length ≥4 cm and ≤ 15 cm

Table 20: Primary Rates at 1 Year by Gender and Geography (ITT Population)

Measure	Gender	Geography	Test DCB %(n/N)	Control PTA %(n/N)	Difference %(n/N)
Freedom from Primary Safety Event[1]	Female	All	80.4% (90/112)	67.4% (31/46)	13.0%
		OUS	94.1% (32/34)	43.8% (7/16)	50.4%
		US	74.4% (58/78)	80.0% (24/30)	-5.6%
	Male	All	86.2% (150/174)	84.5% (82/97)	1.7%
		OUS	86.1% (62/72)	83.8% (31/37)	2.3%
		US	86.3% (88/102)	85.0% (51/60)	1.3%
Primary Patency[2]	Female	All	56.4% (57/101)	61.4% (27/44)	-4.9%
		OUS	70.0% (21/30)	47.1% (8/17)	22.9%
		US	50.7% (36/71)	70.4% (19/27)	-19.7%
	Male	All	70.6% (115/163)	48.4% (44/91)	22.2%
		OUS	68.7% (46/67)	45.5% (15/33)	13.2%
		US	71.9% (69/96)	50.0% (29/58)	21.9%

Although this is a randomized trial, the sample size is relatively small so that subgroup analysis may produce subgroups with considerable imbalance in key predictive covariates. FDA performed a propensity score analysis to assess the impact of potential confounders on the gender results. Covariates pre-specified in the protocol, which may have a potential impact on the study outcome, were all included in the propensity score modeling. These covariates were age, smoking status (current vs. previous/never smoke), obesity (BMI≥30), hypercholesterolemia, diabetes mellitus, total target lesion length (core-lab), maximum percent stenosis of target lesion (core-lab), previous target limb intervention, ankle brachial index (ABI) of target limb, and Rutherford grade. Table 21 shows the covariate distributions between the two randomized treatment groups within the 'US Females' and the 'US Males.' It seems that there were imbalances in some patient characteristics between the two treatment groups within the 'US Female' and the 'US Male' groups. In particular, the "US Female' test group had a higher ABI (p=0.08) compared to the control group which would be expected to favor the test arm. The 'US Male' test group had a slightly lower age of approximately 2 years (p=0.08) and had significantly more patients with previous target lesion interventions compared to the control group (23.7% vs. 9.0%, p=0.02). The clinical significance of these differences between the test and control arms of the 'US Male' group is not clear.

Figure 10 and Figure 11 show the distributions of propensity scores between the treatment groups in the 'US Female' and the 'US Male' groups, respectively. The propensity score distributions overlap relatively well between the treatment groups for both male and female.

Subsequently, patients were grouped into quartile (due to small sample size) according to their propensity scores, and the overall treatment effect across the quartiles for the primary endpoint rates were estimated using inverse variance as weight. Table 22 compares the primary endpoints rates with and without using the propensity scores. In the 'US Female' group, the primary safety endpoint (freedom from the primary safety event) was 77.4% for the LUTONIX DCB and 81.2% for the Control PTA after adjusting for the propensity score; the primary patency rate at 1 year after the propensity score adjustment was 52.4% for the LUTONIX DCB and 76.3% for the Control PTA.

The sponsor suggested that the 'US Female' group had higher proportions of patients with smaller reference vessel diameters and popliteal lesions in the LUTONIX DCB arm compared to the PTA arm and speculated that these differences in allocation may have contributed to the differential treatment effect.

Table 21: Baseline and Demographic Distributions of Subjects by Treatment Groups for US Female and US Male (ITT Population)

Variable	Test DCB %(n/N)	Control PTA %(n/N)	P-value
US Female (n=85 LUTONIX DCB vs. 35 Control PTA)			
Age (mean±SD)	71.3±10.2	72.0±9.6	0.73
Smoking (current smoker)	24.7% (21/85)	22.9% (8/35)	>0.99
Obesity (BMI≥30)	37.7% (32/85)	28.6% (10/35)	0.40
Hypercholesterolemia	90.6% (77/85)	91.4% (32/35)	>0.99
Diabetes mellitus	52.9% (45/85)	54.3% (19/35)	>0.99
Total target lesion length (mm, core-lab), (mean±SD)	64.4±43.2	70.3±44.3	0.51
Maximum percent stenosis, %DS (mean±SD)	77.0±15.5	77.1±13.8	0.99
Previous target lesion limb intervention	24.7% (21/85)	25.7% (9/35)	>0.99
ABI of target limb (mean±SD)	0.74±0.18	0.68±0.14	0.08
Rutherford grade 2 3 4	 23.5% (20/85) 58.8% (50/85) 17.7% (15/85)	 25.7% (9/35) 65.7% (23/35) 8.6% (3/35)	0.47
US Male (n=114 LUTONIX DCB vs. 67 Control PTA)			
Age (mean±SD)	65.7±9.3	67.7±8.9	0.08
Smoking (current smoker)	30.7% (35/114)	40.3% (27/67)	0.20
Obesity (BMI≥30)	41.2% (47/114)	40.3% (27/67)	>0.99
Hypercholesterolemia	95.6% (109/114)	91.0% (61/67)	0.33
Diabetes mellitus	46.5% (53/114)	40.3% (27/67)	0.44
Total target lesion length (mm, core-lab), (mean±SD)	62.1±41.1	63.6±39.1	0.76
Maximum percent stenosis, %DS (mean±SD)	81.3±14.7	81.9±15.3	0.76
Previous target lesion limb intervention	23.7% (27/114)	9.0% (6/67)	0.02
ABI of target limb (mean±SD)	0.76±0.20	0.75±0.18	0.78
Rutherford grade 2 3 4	 37.5% (45/114) 53.5% (61/114) 7.0% (8/114)	 37.3% (25/67) 50.8% (34/67) 11.9% (8/67)	0.54

* P-values are two-sided and calculated using Fisher's exact test for categorical variables and t-test for continuous variables.

Figure 10: Distribution of Propensity Scores by Treatment Groups (US Female)

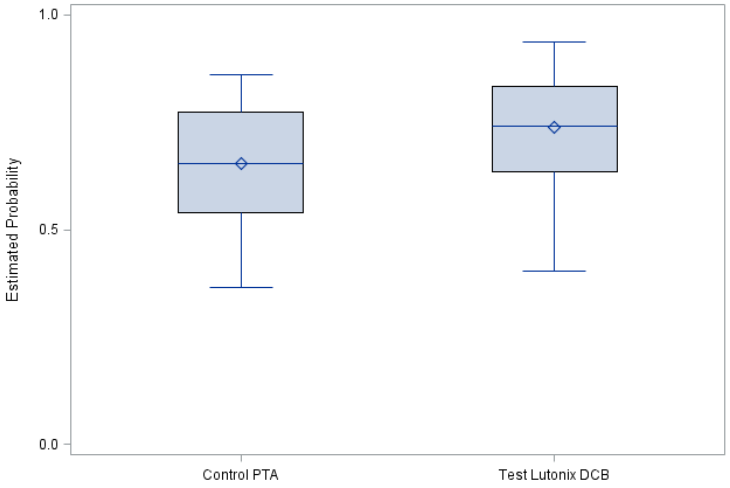


Figure 11: Distribution of Propensity Scores by Treatment Groups (US Male)

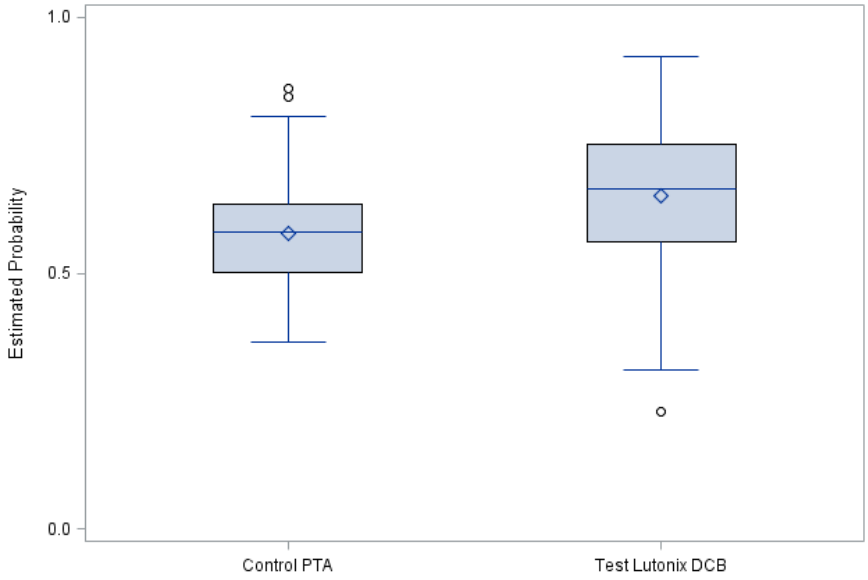


Table 22: Propensity Score Adjusted Primary Endpoint Rates* at 1 Year within US Female and US Male (ITT Population)

Population	Endpoint	Test DCB Adjusted %	Control PTA Adjusted %	Adjusted Difference %	Unadjusted Difference %
US Female	Freedom from Primary Safety Event	74.8%	77.4%	-2.6%	-5.6%
	Primary Patency	50.8%	63.9%	-13.1%	-19.7%
US Male	Freedom from Primary Safety Event	87.6%	86.3%	1.3%	1.3%
	Primary Patency	81.2%	49.8%	31.4%	21.9%

* Overall rates are adjusted using inverse variance method.

In order to better understand the effect of gender and geography, the sponsor was asked to perform a post-hoc breakout all of their available clinical data (pivotal study and continued access registry) by both gender and geography. Although these were statistically planned analyses, these tables may provide clinically relevant insights. As shown in Table 23 and Table 24, the pivotal trial had a large difference in results between US and OUS females, whereas the males had similar results. However, when pooling the available data, the differences in geography by gender are less pronounced.

Table 23: Composite Safety Endpoint Success Rates at 1 year by Gender and Geography (All DCB Population)

	US				**OUS**			
Gender	**Roll-in DCB %(n/N)**	**Randomized DCB %(n/N)**	**Continued Access %(n/N)**	**All DCB %(n/N)**	**Roll-in DCB %(n/N)**	**Randomized DCB %(n/N)**	**Continued Access %(n/N)**	**All DCB %(n/N)**
Female	100.0% (15/15)	74.4% (58/78)	97.6% (40/41)	84.3% (113/134)	75.0% (3/4)	94.1% (32/34)	97.7% (42/43)	95.1% (77/81)
Male	94.7% (18/19)	86.3% (88/102)	98.3% (58/59)	91.1% (164/180)	77.8% (7/9)	86.1% (62/72)	98.8% (84/85)	92.2% (153/166)

[1] Composite freedom from Safety Events, including all-cause peri-operative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.

Table 24: Primary Patency Rates at 1 year by Gender and Geography (All DCB Population)

	US Primary Patency – 1 Year				**OUS Primary Patency – 1 Year**			
Gender	**Roll-in DCB %(n/N)**	**Randomized DCB %(n/N)**	**Continued Access %(n/N)**	**All DCB %(n/N)**	**Roll-in DCB %(n/N)**	**Randomized DCB %(n/N)**	**Continued Access %(n/N)**	**All DCB %(n/N)**
Female	85.7% (12/14)	50.7% (36/71)	32.4% (12/37)	49.2% (60/122)	25.0% (1/4)	70.0% (21/30)	42.9% (15/35)	53.6% (37/69)
Male	65.0% (13/20)	71.9% (69/96)	53.8% (28/52)	65.5% (110/168)	75.0% (6/8)	68.7% (46/67)	52.2% (36/69)	61.1% (88/144)

[1] Primary Patency is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR). CIs for groups and difference are asymptotic.

FDA Comment:

1. An interaction with geography was observed for both primary safety (p=0.02) and primary effectiveness (p=0.12). Based on the three-way interaction test for geography, gender and treatment group, these differences in geography seem to be due to the differences between the US and the OUS female (p=0.001 and 0.10 for the primary safety and the primary effectiveness endpoints, respectively). The panel will be asked to comment on the poolability of the OUS and US data given these results.
2. For US females, the PTA arm performed better than the LUTONIX DCB arm in both the primary safety (80.0% vs. 74.4%, respectively) and the primary patency (70.4% vs 50.7%, respectively). ABI of target limb was the only factor that was not balanced between the two randomized treatment groups with target limb ABI higher in the DCB arm (0.74) compared to the PTA arm (0.68). Even after adjusting for potential confounding covariates, the PTA arm still performed better than LUTONIX DCB in both the primary safety (77.4% vs. 74.8% adjusted, respectively) and the primary patency at 1 year (63.9% vs. 50.8% adjusted, respectively). The panel will be asked to comment on this issue.

Investigational sites with 5 or less subjects were pooled to form "other" sites. There was no interaction detected between sites and treatment group for the primary safety endpoint (p>0.99); also, there was no significant interaction detected for the primary effectiveness endpoint (p=0.97).

In addition to the analyses for gender and geography, the primary endpoints were analyzed using the ITT population for the following pre-specified subgroups (see Table 25 and Table 26):

- Bailout stent status (with versus without)
- VIVA OPC entry criteria (lesion(s) terminates in SFA or proximal popliteal, lesion length ≥4 cm and ≤ 15 cm)
- Total Occlusion (CTO) at baseline
- Lesion length (by quartiles) and separately for long lesions ≥12 cm and ≥14 cm.

- Lesion location by location of most distal treatment area (terminates in proximal SFA, mid SFA, distal SFA, proximal popliteal, mid popliteal, distal popliteal) and separately by all treated segments entirely within the SFA only, both SFA and popliteal, popliteal only.
- Single balloon versus multiple balloon use.

Table 25: Primary Safety Endpoint Success Rate[1] at 1 year by Subgroup (ITT Population)

Variable	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]
Bailout Stent Status	With bailout stenting	85.7% (6/7) [59.8, 100.0]	75.0% (9/12) [50.5, 99.5]	10.7% [-28.4, 49.8]
	Without bailout stenting	83.9% (234/279) [79.6, 88.2]	79.4% (104/131) [72.5, 86.3]	4.5% [-3.2, 12.1]
Meets VIVA OPC Entry Criteria	No	82.0% (73/89) [74.0, 90.0]	80.5% (33/41) [68.4, 92.6]	1.5% [-12.3, 15.4]
	Yes	84.8% (167/197) [79.8, 89.8]	78.4% (80/102) [70.4, 86.4]	6.3% [-2.5, 15.2]
Chronic Total Occlusion	No	85.1% (194/228) [80.5, 89.7]	76.4% (84/110) [68.4, 84.3]	8.7% [0.3, 17.2]
	Yes	79.3% (46/58) [68.9, 89.7]	87.9% (29/33) [76.7, 99.0]	-8.6% [-24.2, 7.1]
Lesion Length Quartile	Q1: <30	84.3% (59/70) [75.8, 92.8]	78.8% (26/33) [64.8, 92.7]	5.5% [-9.7, 20.7]
	Q2: 30-52	81.1% (60/74) [72.2, 90.0]	86.1% (31/36) [74.8, 97.4]	-5.0% [-19.4, 9.4]
	Q3: 52-94	88.7% (63/71) [81.4, 96.1]	77.8% (28/36) [64.2, 91.4]	11.0% [-3.1, 25.0]
	Q4: ≥94	81.4% (57/70) [72.3, 90.5]	73.7% (28/38) [59.7, 87.7]	7.7% [-8.1, 23.6]
Lesion Length ≥ 12 cm	No	85.0% (215/253) [80.6, 89.4]	78.6% (99/126) [71.4, 85.7]	6.4% [-1.4, 14.2]
	Yes	75.0% (24/32) [60.0, 90.0]	82.4% (14/17) [64.2, 100.0]	-7.4% [-31.2, 16.5]
Lesion Length ≥ 14 cm	No	84.3% (225/267) [79.9, 88.6]	79.3% (107/135) [72.4, 86.1]	5.0% [-2.6, 12.6]
	Yes	77.8% (14/18) [58.6, 97.0]	75.0% (6/8) [45.0, 100.0]	2.8% [-31.3, 36.9]
Most Distal Lesion Location	Proximal SFA	80.0% (20/25) [64.3, 95.7]	92.3% (12/13) [77.8, 100.0]	-12.3% [-35.3, 10.7]
	Mid SFA	85.6% (131/153) [80.1, 91.2]	79.1% (53/67) [69.4, 88.8]	6.5% [-3.7, 16.8]
	Distal SFA	85.2% (69/81) [77.4, 92.9]	75.0% (39/52) [63.2, 86.8]	10.2% [-3.3, 23.7]
	Proximal Popliteal	93.3% (14/15) [80.7, 100.0]	100.0% (6/6) [100.0, 100.0]	-6.7% [-17.7, 4.4]
	Mid Popliteal	50.0% (5/10) [19.0, 81.0]	75.0% (3/4) [32.6, 100.0]	-25.0% [-81.9, 31.9]
	Distal Popliteal	50.0% (1/2) [0.0, 100.0]	0.0% (0/1) [0.0, 0.0]	50.0% [-64.9, 100.0]

Variable	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]
Lesion Location	Popliteal	73.1% (19/26) [56.0, 90.1]	88.9% (8/9) [68.4, 100.0]	-15.8% [-46.1, 14.5]
	SFA	84.9% (220/259) [80.6, 89.3]	78.8% (104/132) [71.8, 85.8]	6.2% [-1.5, 13.8]
	SFA and Popliteal	100.0% (1/1) [100.0, 100.0]	50.0% (1/2) [0.0, 100.0]	50.0% [-64.9, 100.0]
Number of Balloons	Multiple	83.3% (85/102) [76.1, 90.6]	76.5% (13/17) [56.3, 96.6]	6.9% [-11.2, 24.9]
	Single	84.2% (155/184) [79.0, 89.5]	79.4% (100/126) [72.3, 86.4]	4.9% [-3.7, 13.4]

[1] Composite of freedom from all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
[2] CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. CI for differences are provided without adjustment for multiplicity.

Table 26: Primary Patency Rate[1] at 1 year by Subgroup (ITT Population)

Variable	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]
Bailout Stent Status	With bailout stenting	83.3% (5/6) [53.5, 100.0]	41.7% (5/12) [13.8, 69.6]	41.7% [0.8, 82.5]
	Without bailout stenting	64.7% (167/258) [58.9, 70.6]	53.7% (66/123) [44.8, 62.5]	11.1% [0.5, 21.6]
Meets VIVA OPC Entry Criteria	No	68.8% (55/80) [58.6, 78.9]	60.0% (24/40) [44.8, 75.2]	8.8% [-9.5, 27.0]
	Yes	63.6% (117/184) [56.6, 70.5]	49.5% (47/95) [39.4, 59.5]	14.1% [1.9, 26.3]
Chronic Total Occlusion	No	68.1% (143/210) [61.8, 74.4]	58.7% (61/104) [49.2, 68.1]	9.4% [-1.9, 20.8]
	Yes	53.7% (29/54) [40.4, 67.0]	32.3% (10/31) [15.8, 48.7]	21.4% [0.3, 42.6]
Lesion Length Quartile	Q1: <30	72.3% (47/65) [61.4, 83.2]	60.6% (20/33) [43.9, 77.3]	11.7% [-8.2, 31.6]
	Q2: 30-52	64.7% (44/68) [53.3, 76.1]	64.7% (22/34) [48.6, 80.8]	0.0% [-19.7, 19.7]
	Q3: 52-94	69.2% (45/65) [58.0, 80.5]	45.7% (16/35) [29.2, 62.2]	23.5% [3.6, 43.5]
	Q4: ≥94	53.8% (35/65) [41.7, 66.0]	39.4% (13/33) [22.7, 56.1]	14.5% [-6.2, 35.1]
Lesion Length ≥ 12 cm	No	67.2% (156/232) [61.2, 73.3]	53.7% (65/121) [44.8, 62.6]	13.5% [2.8, 24.3]
	Yes	48.4% (15/31) [30.8, 66.0]	42.9% (6/14) [16.9, 68.8]	5.5% [-25.8, 36.9]
Lesion Length ≥ 14 cm	No	66.8% (165/247) [60.9, 72.7]	52.3% (67/128) [43.7, 61.0]	14.5% [4.0, 24.9]
	Yes	37.5% (6/16) [13.8, 61.2]	57.1% (4/7) [20.5, 93.8]	-19.6% [-63.3, 24.0]

Variable	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]
Most Distal Lesion Location	Proximal SFA	62.5% (15/24) [43.1, 81.9]	53.8% (7/13) [26.7, 80.9]	8.7% [-24.7, 42.0]
	Mid SFA	67.9% (95/140) [60.1, 75.6]	52.4% (33/63) [40.0, 64.7]	15.5% [0.9, 30.0]
	Distal SFA	65.3% (49/75) [54.6, 76.1]	50.0% (24/48) [35.9, 64.1]	15.3% [-2.4, 33.1]
	Proximal Popliteal	71.4% (10/14) [47.8, 95.1]	83.3% (5/6) [53.5, 100.0]	-11.9% [-50.0, 26.2]
	Mid Popliteal	30.0% (3/10) [1.6, 58.4]	50.0% (2/4) [1.0, 99.0]	-20.0% [-76.6, 36.6]
	Distal Popliteal	0.0% (0/1) [0.0, 0.0]	0.0% (0/1) [0.0, 0.0]	0.0%
Lesion Location	Popliteal	50.0% (12/24) [30.0, 70.0]	66.7% (6/9) [35.9, 97.5]	-16.7% [-53.4, 20.1]
	SFA	66.5% (159/239) [60.5, 72.5]	51.6% (64/124) [42.8, 60.4]	14.9% [4.3, 25.6]
	SFA and Popliteal	100.0% (1/1) [100.0, 100.0]	50.0% (1/2) [0.0, 100.0]	50.0% [-19.3, 100.0]
Number of Balloons	Multiple	60.9% (56/92) [50.9, 70.8]	18.8% (3/16) [0.0, 37.9]	42.1% [20.6, 63.7]
	Single	67.4% (116/172) [60.4, 74.4]	57.1% (68/119) [48.3, 66.0]	10.3% [-1.0, 21.6]

[1] Primary Patency is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR). CIs for groups and difference are asymptotic.
[2] CI for difference are provided without adjustment for multiplicity.

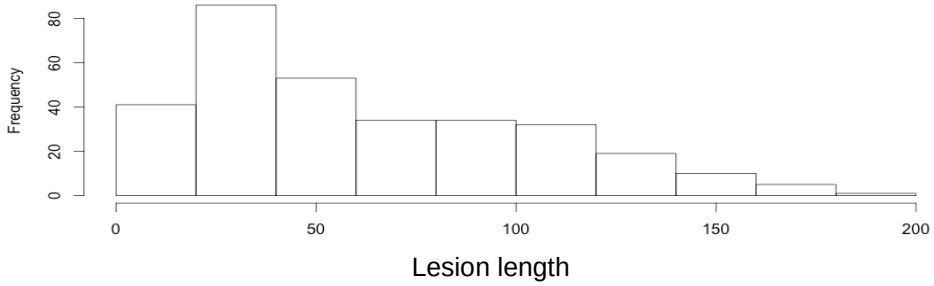
For the primary safety endpoint, there was a qualitative interaction between chronic total occlusion (no vs. yes) and the treatment group (p=0.06). Among those with no chronic occlusion, 85.1% (194/228) of the LUTONIX DCB and 76.4% (84/110) of the Control PTA were free from the primary safety event. However, among those with chronic total occlusion, 79.3%% (46/58) of the LUTONIX DCB and 87.9% (29/33) of the Control PTA were free from the primary safety event. Findings suggest that the PTA arm performed better than the LUTONIX DCB arm with respect to freedom from safety events when treating chronic total occlusions. No other pre-specified subgroup analysis showed significant interaction with the treatment assignment group.

For the primary effectiveness endpoint, there was a qualitative interaction between lesion length ≥ 14 cm and the treatment group (p=0.13) and a quantitative interaction between number of balloons (multiple vs. single) used and the treatment groups (p=0.03). For those with lesion length < 14 cm, 66.8% (165/247) of the LUTONIX DCB and 52.3% (67/128) had primary patency at 1 year; whereas for those with lesion length ≥ 14 cm, 37.5% (6/16) of the LUTONIX DCB and 57.1% (4/7) of the Control PTA had the primary patency at 1 year. Findings suggest that the PTA arm performed better than the LUTONIX DCB arm with regards to primary patency in long lesions (≥14cm); however, the clinical significance of this difference is uncertain given the small sample of patients with lesion lengths ≥ 14 cm. For those who use multiple balloons during the procedure, 60.9% (56/92) of the LUTONIX DCB and 18.8% (3/16) of the Control PTA had the primary patency at 1 year; for those who used single balloon, 67.4% (116/172) of the LUTONIX DCB and 57.1% (68/119) of the Control PTA had the primary patency at 1 year. The disproportionate increased use of multiple balloons in the test arm would be expected given that the same balloon may not be advanced to treat a different portion of the

vessel segment. No other pre-specified subgroup showed interaction with the treatment group.

The average total lesion length (sum of treated lesions) for the test arm in LEVANT 2 was 62.7 ± 41.4mm (n=315). However, 40% of the data came from patients with lesions ≤40mm in length. The histogram demonstrates frequency of the lesions lengths treated with the LUTONIX DCB.

Table 27: Occurrence of Lesion Lengths



FDA Comment: Given that the vast majority of the data was collected on relatively short lesions, these results indicating a difference in short and long lesions raise questions regarding the applicability of the study conclusions for the full range of proposed lesion lengths (up to 15 cm). The panel will be asked to comment on this issue.

5.2.8 Device Success, Utility & Malfunction

The sponsor reported comparable rates of device, technical and procedural success with their device (see Table 28).

Table 28: Device, Technical, and Procedural Success (ITT Population)

Variable	Test DCB	Control PTA	P-value	Pooled
Device Success, % (n/N)	99.5% (430/432)	100% (180/180)	0.361	99.6% (508/510)
Technical Success (Core Lab, All Lesions), % (n/N)	89.2% (282/316)	86.8% (138/159)	0.431	88.4% (420/475)
Procedural Success (Core Lab, All Lesions), % (n/N)	88.9% (281/316)	86.8% (138/159)	0.497	88.2% (419/475)

1. *Device Success* - successful delivery and deployment of the study device(s) as intended at the intended target lesion, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system. If a device is inserted into the subject but not used due to user error (e.g. inappropriate balloon length or transit time too long), this device will not be included in the device success assessment.
2. *Technical Success* - successful access and deployment of the device and visual estimate of ≤30% diameter residual stenosis during the index procedure without deployment of a bailout stent.
3. *Procedural Success* - attainment of ≤30% residual stenosis in the treatment area by independent core lab analysis without serious adverse events during the index procedure.

5.2.9 Pharmacokinetic Evaluation

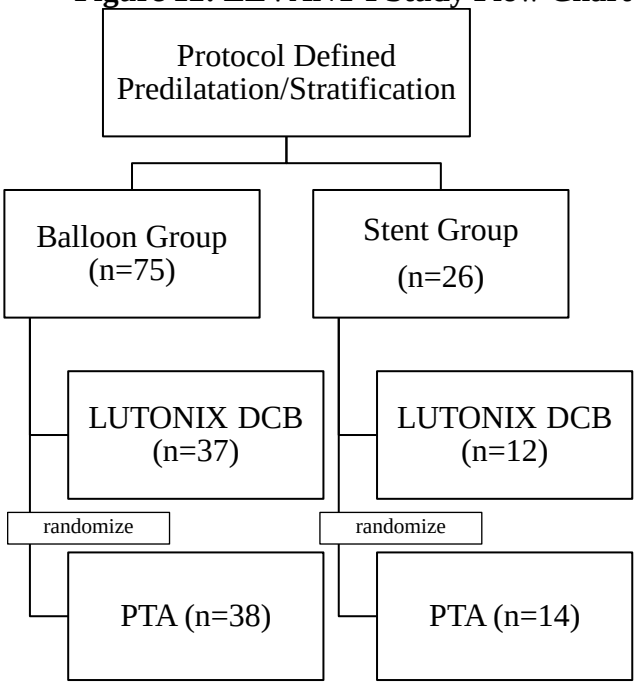
Pharmacokinetics analysis was performed in a subset of patients randomized to the LUTONIX DCB catheter arm in the LEVANT 2 clinical study (n=22 subjects) who received varied doses in the 1.3 mg – 5 mg range. All subjects had detectable serum paclitaxel immediately after the

index procedure that decreased to less than 3 ng/mL within one hour. The pharmacokinetics of paclitaxel following LUTONIX DCB treatment generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Following LUTONIX DCB catheter treatment, the group mean (SD) values for the pharmacokinetic parameters C_{max}, AUC_{all}, and MRT_{last} were 5.10 (3.21) ng/mL, 8.39 (4.00) ng*h/mL, and 2.13 (1.84) h, respectively.

5.3 LEVANT 1 Study/Design Results

The LEVANT I Trial was a prospective multicenter randomized trial comparing the LUTONIX DCB (earlier Model 9003) to standard balloon angioplasty for treatment of femoropopliteal arteries with and without stenting. Patients were enrolled who had clinical evidence of claudication or critical limb ischemia (CLI) and an angiographically significant lesion in the femoropopliteal arteries. After pre-dilatation, subjects were stratified based on pre-defined criteria (see Figure 12).

Figure 12: LEVANT I Study Flow Chart



The primary endpoint was angiographic late lumen loss at 6 months and follow-up was obtained to 24 months. At 6 months, the LUTONIX DCB demonstrated significant improvement compared to PTA alone in the Balloon Group, but did not demonstrate significant comparative improvement in the Stent Group (see Table 29).

Table 29: LEVANT 1 Study Results

	12 Months		24 Months	
	LUTONIX % (n/N)	**POBA % (n/N)**	**LUTONIX % (n/N)**	**POBA % (n/N)**
Primary Patency (DUS PSVR ≥ 2.5)	**66.7% (30/45)**	**54.8% (23/42)**	**57.1% (24/42)**	**39.5% (17/43)**
Target Lesion Revascularization (TLR)	28.9% (13/45)	33.3% (14/42)	35.7% (15/42)	48.8% (20/41)
Adverse Events	**LUTONIX Catheter N=49 n (total events)**	**POBA N=52 n (total events)**	**LUTONIX Catheter N=49 n (total events)**	**POBA N=52 n (total events)**
Non-serious AE[1]	23 (32)	29 (51)	28 (50)	31 (74)
SAE[1]	33 (66)	34 (80)	39 (90)	39 (110)
Thrombosis (target vessel)	0 (0)	1 (1)	0	1 (1)
Amputation	1 (1)	0 (0)	1	0 (0)
Death	3 (3)	4 (4)	4	5 (5)
TLR	13 (17)	14 (14)	15 (20)	20 (21)
TVR	13 (17)	15 (19)	15 (20)	21 (26)

1. Any given subject may have more than one reported AE or SAE. SAEs reported at 24 Months follow-up that occurred within the 12 Month follow-up time window (395 days) are included at 12 Months.

FDA Comment: Overall, the LEVANT I results indicate that the LUTONIX DCB demonstrated comparable safety and improved late lumen loss compared to PTA alone.

5.4 Safety Registry

The Safety Registry consists of two components, a Continued Access Study, conducted at LEVANT 2 study sites and additional safety data collected at sites that were not included in LEVANT 2 study. The purpose of the Safety Registry is to evaluate the rate of unanticipated device- or drug- related adverse events over time through 60 months. To date, 657 subjects were enrolled at 63 sites in the US and Europe. Approximately, 99%, 82% and 35% of patients have completed 30-day, 6-month and 12-month follow-up, respectively. The Registry includes the same patient population, medical regimen, follow-up schedule, definitions and study device as the LEVANT 2 trial. The primary endpoint is the rate of unanticipated device- or drug-related adverse events through 60 months. The study is designed to detect adverse events in the 1-2% range when evaluating the combined data from the LEVANT 2 trial (roll-in, randomized) and the data from prospectively enrolling Safety Registry.

An evaluable sample size of 869 test subjects was required for the following: If the observed rare adverse event rate is 1%, then the upper limit of the 95% Confidence Interval is 1.8% (PASS2008: Exact Clopper-Pearson). Assuming an expected 1% incidence rate, Power is > 95% to observe at least 4 unexpected SAEs (PASS2008: Post-Marketing Surveillance). Similarly, if the observed rate is 2%, then the upper limit of the 95% Confidence Interval is 3.0%. Assuming an expected 2% incidence rate, Power is > 95% to observe at least 11 unexpected SAEs.

To date, the composite safety evaluation of the LUTONIX DCB patient experience did not yield any rare or unanticipated adverse events associated with the use of the LUTONIX DCB. Multiple

secondary safety and effectiveness endpoints are also being captured including the assessment of primary patency. The sponsor provided interim results from primary patency at 6 and 12 months (see Table 30).

FDA had requested that at the time of the PMA submission, the sponsor provide 12-month data on at least 50% of the total safety cohort and then provide an update with the near-complete data set prior to the panel meeting. However, Lutonix did not provide the requested quantity of data. As of the last provided report for the LEVANT 2 Safety Registry, only 29.4% (193/657) and 34.7% (228/657) of subjects have evaluable data available for primary patency and composite safety endpoint analyses, respectively at the 12-month follow-up. This data will be combined with the drug coated balloon subjects from the LEVANT 2 Randomized trial to statistically evaluate the primary endpoint.

FDA Comment: When combined with the LEVANT 2 Randomized DCB cohort, Lutonix has only provided safety data on 561 patients of the 1022 patients enrolled which does not meet the minimum sample size (n=869) needed to statistically evaluate rare adverse events. Thus there are limited data to draw conclusions about the potential for rare adverse safety events associated with the drug or the particulates that embolize during the procedure. The Panel will be asked to discuss this issue.

Table 30: Primary Patency at 6-Months and 12-Months for all DCB in Safety Registry

Primary Patency[1]	Roll-in DCB %(n/N) [95% CI[2]]	Randomized DCB %(n/N) [95% CI]	Continued Access %(n/N) [95% CI]	All DCB %(n/N) [95% CI]
6-Month	77.1% (37/48) [65.2, 89.0]	81.2% (225/277) [76.6, 85.8]	81.4% (354/435) [77.7, 85.0]	81.1% (616/760) [78.3, 83.8]
12-Month	69.6% (32/46) [56.3, 82.9]	65.2% (172/264) [59.4, 70.9]	47.2% (91/193) [40.1, 54.2]	58.6% (295/503) [54.3, 63.0]

1. Primary Patency is defined as freedom from target lesion restenosis (defined by core lab adjudication) and target lesion revascularization (TLR).
2. Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.

Additionally, the sponsor provided information on primary patency from all available LUTONIX DCB subjects as shown in Table 31.

Table 31: 12-Month Primary Patency from Combined Trials

Data Set	Primary Patency Results		Difference % [95% CI]	P-value
	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]		
LEVANT 2 Study (ITT)	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.02
LEVANT 2 Study (PP)	65.3% (160/245) [59.3, 71.3]	56.0% (56/100) [46.3, 65.7]	9.3% [-2.1, 20.7]	0.11
LEVANT 2 Study: Roll-Ins	69.6% (32/46) [56.3, 82.9]			
LEVANT 2 Safety Registry	47.2% (91/193) [40.1, 54.2]			
ALL DCB	58.6% (295/503) [54.3, 63.0]			

As of the last available update, only 193 patients have reached the 12-month endpoint and are evaluable for primary patency. The sponsor notes that the lower patency rate at 12 months for the LEVANT 2 Safety Registry is due to the fact that follow-up in ongoing. Specifically, all known failures are counted against the primary endpoint even if the patient has not reached the 12-month follow-up timepoint; however, successes are sensored until the patient reaches the 12-month timepoint; thus resulting in a disproportionate counting of failures and successes.

5.5 Global Registry

The Global SFA Registry is a post-market registry intended to demonstrate safety and assess the clinical use and outcomes of the LUTONIX DCB in a real-word environment. There is planned enrollment of 1,000 patients with follow up for a minimum of 2 years to primarily evaluate TLR at 12 months and 30-day safety events . Only 7 patients have been followed to the 12-month endpoint; therefore, primary endpoint results are not available. Preliminary safety information from the 437 patients enrolled indicates that the most frequent SAEs are pseudoaneurysm (0.7%, 3/437) and Occlusion/Closure (0.7%, 3/437). No significant safety trends were noted with the limited data reported to date.

5.6 Summary of Total Clinical Experience

Data are available from multiple clinical experiences. The summary of the total clinical experience with the LUTONIX DCB is presented in Table 32, Table 33, and Table 34.

Table 32: Summary of the Total Clinical Experience with the LUTONIX DCB

Visit	LEVANT 1 n=49 n(%)	LEVANT 2 Randomized		LEVANT 2 Continued Access Test DCB n=657 n(%)	Global SFA Registry Test DCB n=437 n(%)	Total Follow-Up to Date Test DCB Only
		Roll-In n=56 n(%)	Rand. n=316 n(%)			
1m	49 (100%)	55 (98.2%)	313 (99.1%)	649 (98.8%)	340 (77.8%)	**1406**
6m	47 (96%)	52 (92.9%)	293 (92.7%)	541 (82.3%)	126 (28.8%)	**1059**
12m	45 (92%)	46 (82.1%)	280 (88.6%)	227 (34.6%)	7 (1.6%)	**605**
24m	41 (84%)	32 (57.1%)	125 (39.6%)	0/0 (0%)	0/0 (0%)	**198**
36m	NA	0 (0%)	0 (0%)	0 (0%)	Pts consented to 5 yrs	**0**
48m		0 (0%)	0 (0%)	0 (0%)		**0**
60m		0 (0%)	0 (0%)	0 (0%)		**0**

Table 33: 12-Month Safety from Combined Trials

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
LEVANT 2 ITT Primary Safety[1]	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-2.6, 12.3]	0.005
LEVANT 2 PP (prespecified) Primary Safety[2]	83.7% (221/264) [79.3, 88.2]	83.0% (88/106) [75.9, 90.2]	0.7% [-7.3, 8.7]	0.080
LEVANT 2 Roll-Ins	91.5% (43/47) [83.5, 99.5]			
LEVANT 2 Safety Registry[4]	98.2% (224/228) [96.5, 99.9]			
ALL DCB (LEVANT 2 ITT RCT, LEVANT 2 Roll-in, Safety Registry)	90.4% (507/561) [87.9, 92.8]			

Safety Event (subject may have more than one event)	Roll-in DCB %(n/N) [95% CI]	Randomized DCB LEVANT 2 %(n/N) [95% CI]	Continued Access %(n/N) [95% CI]	All DCB %(n/N) [95% CI]	Control PTA LEVANT 2 %(n/N) [95% CI]
Perioperative (<=30) Death	0.0% (0/54) [0.0, 0.0]	0.0% (0/308) [0.0, 0.0]	0.2% (1/623) [0.0, 0.5]	0.1% (1/985) [0.0, 0.3]	0.0% (0/155) [0.0, 0.0]
Index Limb Related Death at 12 Months	0.0% (0/47) [0.0, 0.0]	0.0% (0/285) [0.0, 0.0]	0.0% (0/227) [0.0, 0.0]	0.0% (0/559) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]
Amputation at 12 Months	0.0% (0/47) [0.0, 0.0]	0.3% (1/286) [0.0, 1.0]	0.0% (0/227) [0.0, 0.0]	0.2% (1/560) [0.0, 0.5]	0.0% (0/140) [0.0, 0.0]
Target Limb Revascularization 12 months	8.5% (4/47) [0.5, 16.5]	15.4% (44/285) [11.2, 19.6]	1.3% (3/227) [0.0, 2.8]	9.1% (51/559) [6.7, 11.5]	21.0% (30/143) [14.3, 27.7]

1. Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
2. PP Population prespecified to exclude core lab geographic miss, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization, site reported length > 150mm.
3. PP2 Population specified post-hoc to exclude core lab lesions length >150mm and diameter < 4mm, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization.

Table 34: 12-Month Primary Patency from Combined Trials

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
LEVANT 2 ITT Primary Patency[1]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
LEVANT 2 PP (prespecified) Primary Patency[2]	65.3% (160/245) [59.3, 71.3]	56.0% (56/100) [46.3, 65.7]	9.3% [-2.1, 20.7]	0.107
LEVANT 2 Roll-Ins	69.6% (32/46) [56.3, 82.9]			
LEVANT 2 Safety Registry[4]	47.2% (91/193) [40.1, 54.2]			
ALL DCB	58.6% (295/503) [54.3, 63.0]			

Time	Roll-in DCB %(n/N) [95% CI]	Randomized DCB %(n/N) [95% CI]	Continued Access %(n/N) [95% CI]	All DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]
6 Months	77.1% (37/48) [65.2, 89.0]	81.2% (225/277) [76.6, 85.8]	81.4% (354/435) [77.7, 85.0]	81.1% (616/760) [78.3, 83.8]	
12 Months	69.6% (32/46) [56.3, 82.9]	65.2% (172/264) [59.4, 70.9]	47.2% (91/193) [40.1, 54.2]	58.6% (295/503) [54.3, 63.0]	52.6% (71/135) [44.2, 61.0]

1. Primary Patency is defined freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
2. PP Population prespecified to exclude core lab geographic miss, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization, site reported length > 150mm.
3. PP2 Population defined post-hoc to exclude core lab lesions length >150mm and diameter < 4mm, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization.
4. Safety Registry includes Continued Access patients (enrolled at LEVANT 2 sites) and Additional Registry patients (enrolled at sites other than LEVANT 2 sites); results at 6-months {81.4% i354/435); [77.7, 85.0]} were similar to the RCT cohort.

6 POST APPROVAL STUDY (PAS)

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The summary provided below is the sponsor's proposal for evaluating the device post-market. FDA's review of this proposal is still ongoing; therefore, this does not represent an agreed upon study design. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

Table 35: Post-Approval Study Overview

Description	Post-Approval Study Plan for the Lutonix 035 Drug Coated Balloon PTA Catheter for Treatment of Stenotic or Obstructive Lesions in the Femoropopliteal Artery
Overview	The objective of the post-approval study plan is to evaluate safety of the Lutonix DCB for rare adverse events over a 5 year period and to reconfirm the superior efficacy and non-inferior safety for treatment of stenosis of the femoropopliteal arteries in a large population of subjects. The primary endpoint of the post-approval study plan is the rate of unanticipated device- or drug- related adverse events over time through 60 months. Hypothesis tested secondary endpoints are superiority of patency endpoint at 24 months and non-inferiority of the composite safety endpoint at 12 months. The LEVANT 2 registry studies (LEVANT 2 Continued Access registry and the LEVANT 2 Safety registry) will provide additional safety and efficacy information from an additional 657 DCB subjects beyond the 372 DCB patients (roll-in & randomized) already in the LEVANT 2 pivotal IDE study. In total, clinical data from 1029 Lutonix DCB subjects will be available from the LEVANT 2 clinical program. Additional safety and efficacy data will also be available from the real-world Lutonix Global SFA Registry study with enrollment up to 1000 subjects.
Sample Size	In total 657 DCB subjects were enrolled in the LEVANT 2 registry studies. These subjects are in addition to the 372 DCB patients from the LEVANT 2 pivotal IDE study, will provide clinical data from total of 1029 Lutonix DCB subjects for post-approval study analysis.
Subject Follow-Up Schedule (LEVANT 2 program)	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 0-30 days, 6 months, 12 months, and 24 months *Telephone:* 1, 36, 48 and 60 Months
Primary Endpoint	Rate of unanticipated device- or drug- related adverse events over time through 60 months
Secondary Endpoints (Hypothesis Tested)	*Efficacy:* Primary Patency of the target lesion at 24 months. Primary Patency is defined as the absence of target lesion restenosis (as adjudicated by core-lab) and freedom from target lesion revascularization (TLR). Superior efficacy will be reconfirmed through pre-specified hypothesis testing of the primary patency at 24 months: All LEVANT 2 Lutonix DCB subjects (n*=1029) vs. pivotal IDE control PTA subjects (n*=160).

	Safety: Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 12 months: index limb amputation, index limb re-intervention, and index-limb-related death. Non-inferiority for safety will be reconfirmed through pre-specified hypothesis testing of the composite safety endpoint at 12 months: LEVANT 2 registry Lutonix DCB subjects (n*=657) vs. pivotal IDE control PTA subjects (n*=160). * without accounting for loss to follow-up

FDA Comment: The post-approval study proposal by Lutonix is still under review by FDA.

1. Keeping in mind all of the issues raised with the existing studies (e.g., potential bias, gender and geography interactions, and the diminished treatment effect at 730 days), the panel will be asked to comment on the adequacy of the proposed post-approval study for long-term follow-up of the existing study cohorts or the need for a new enrollment study.

2. The panel will also be asked to comment if there are additional questions beyond the longer-term performance of LUTONIX DCB that should be evaluated as part of the post-approval study.

7 FDA CONSIDERATIONS AND CONCLUSIONS

Fundamentally, the LEVANT 2 trials was designed to compare two treatment strategies:

1. LUTONIX® 035 Drug Coated Balloon PTA Catheter vs.
2. Standard PTA.

The clinical question linked to the performance of the LUTONIX DCB is whether the study data support use of this device over PTA considering the benefit/risk assessment of adding the drug coating.

When evaluating whether the totality of the data (including the randomized LEVANT 2 Study, the roll-in patients from LEVANT 2, the Safety Registry, the Global Registry, and the LEVANT 1 Study) provide a reasonable assurance of safety and effectiveness of the LUTONIX DCB for the proposed indications, the following points should be considered:

1. Primary Safety Analysis

- LUTONIX DCB is non-inferior to PTA with respect to 12-month freedom from safety events for the prespecified primary ITT analysis (83.9% vs. 79.0%; p=0.005).
- No peri-operative death (< 30 days) or limb-related death (≤ 12 months) was observed. One amputation was observed which occurred in the LUTONIX DCB arm. Target Limb Revascularization at 12 months was the primary contributor to safety events in both arms.

2. Primary Effectiveness Analysis (ITT)

- LUTONIX DCB is superior to PTA with respect to 12-month primary patency for the

prespecified primary ITT analysis (65.2% vs. 52.6%; p=0.015).

3. Supplemental Analyses of Primary Effectiveness and Safety Endpoints

- LUTONIX DCB was not demonstrated to be non-inferior to PTA with respect to 12-month safety for pre-specified PP analysis (83.7% vs. 83.0%; p=0.08).
- LUTONIX DCB is not superior to PTA with respect to 12-month primary patency for pre-specified PP Analysis (65.3% vs. 56.0%; p=0.11).
- The sponsor indicated that the primary reason for the findings from the PP analyses is that there was unbalanced increased exclusion of patients with geographic miss from the PTA arm and that the excluded patients had significant differences in baseline characteristics (e.g., %DS) that correlates with primary endpoint failure.
- When evaluating covariates for the primary effectiveness endpoint, there was a qualitative interaction between lesion length ≥ 14 cm and the treatment group (p=0.13) showing that longer lesions do better in the PTA arm.
- LUTONIX DCB is superior to PTA with respect to 12-month primary patency for restenosis defined at the pre-specified threshold of PSVR ≥ 2.5 (p=0.017). Statistical significance is maintained at the 3.0 threshold (p=0.022); however, there was not a significant difference at the 2.0 threshold (p=0.130).
- The sponsor has obtained inadequate data on patients followed to 12 months to detect rare and/or unanticipated adverse events in the 1-2% range. To date, 12-month evaluable data from 561 patients for safety has been provided of the 869 test subjects required to detect adverse events occurring at a 1-2% rate with sufficient confidence.

4. Secondary Endpoints With Hypothesis Testing

- The sponsor pre-specified nine secondary endpoints with planned hypothesis testing that were to be tested in a hierarchical fashion. The first hypothesis tested, total TLR at 12 months, failed to show that the LUTONIX device was superior to PTA (12.3% vs. 16.8%; p=0.208); therefore, the remaining endpoints were not tested.

5. Subgroup Analyses

- For US Females, the PTA arm performed better than the LUTONIX DCB arm with regard to freedom from primary safety events (80.0% vs. 74.4%) and primary patency (70.4% vs 50.7%). Whereas, for US Males, the LUTONIX DCB arm performed better both with respect to freedom from primary safety events (86.3% vs. 85.0%) and primary patency (71.9% vs. 50.0%).
- Overall, the LUTONIX DCB performed better in the OUS than the US in terms of the freedom from primary safety event rate and the primary patency rate at 1 year; however, this difference may be due to the significant difference in the US and OUS Female results.

6. Bias

- The sponsor included trial elements to minimize bias including: (1) requiring follow-up clinical assessments to be performed by physicians blinded to treatment; (2) patients requiring stenting after predilatation were excluded from randomization; and (3) since reinterventions may be driven by imaging data rather than worsening of clinical symptoms, the clinical status of the subject was to be assessed prior to reviewing the

imaging data. One area of bias that could not be controlled was procedural bias, given that the treatment and control devices were different. Procedural bias may have contributed to the observations that the LUTONIX DCB arm included significant differences compared to the Control group with regard to lower inflation pressures with a trend towards inadequate overstretch as well as reduced use of bail-out stenting. Furthermore, a high number of protocol deviations were observed in both study arms.

7. Device Success/Utility and Malfunction

- The sponsor reported comparable measures for device, technical and procedural success between the study arms. No significant issues regarding device safety and/or performance were noted.

The data presented in the PMA characterize the safety and effectiveness of the LUTONIX DCB when used to treat patients with clinically significant femoropopliteal stenoses who are eligible for treatment. The Advisory Panel will be asked to assess whether these data demonstrate a reasonable assurance of safety and effectiveness and address the benefit-risk profile of the LUTONIX DCB for the improvement of luminal diameter in these vessels. It is critical that Advisory Panel members review the totality of data in making these determinations.

Appendix 1: Secondary Endpoint Results

Table 36. Results of Hypothesis Testing for Secondary Endpoints (ITT Population)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value
12 Month Endpoints				
Total TLR at 12 Months	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]	-4.5% [-11.7, 2.7]	0.208
Total TVR at 12 Months	13.3% (38/285) [9.4, 17.3]	18.2% (26/143) [11.9, 24.5]	-4.8% [-12.3, 2.6]	0.190
Composite Safety Events[2] at 12 Months	16.1% (46/286) [11.8, 20.3]	21.0% (30/143) [14.3, 27.7]	-4.9% [-12.8, 3.0]	0.215
24 month Endpoints – INTERIM ANALYSIS				
Composite Events[2] at 24 months (non-inferiority test)	31.8% (50/157) [24.6, 39.1]	43.2% (35/81) [32.4, 54.0]	-11.4% [-24.4, 1.7]	0.006
Primary Patency at 24 months	31.8% (49/154) [24.5, 39.2]	20.0% (17/85) [11.5, 28.5]	11.8% [0.6, 23.1]	0.047
Total TLR at 24 months	26.7% (40/150) [19.6, 33.7]	35.9% (28/78) [25.3, 46.5]	-9.2% [-22.0, 3.6]	0.151
TVR at 24 months	28.3% (43/152) [21.1, 35.4]	39.2% (31/79) [28.5, 50.0]	-11.0% [-23.9, 2.0]	0.093
Composite Events[2] at 24 months (superiority test)	31.8% (50/157) [24.6, 39.1]	43.2% (35/81) [32.4, 54.0]	-11.4% [-24.4, 1.7]	0.085
Target-Limb-Related Hospital Days at 24 months	Not Available Admission and discharge dates were not captured in the eCRF or monitored. Analysis will be reported in the 24 month Report.			

Table 37. Secondary Efficacy Endpoints by Timepoint (ITT Population)

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value
Primary Patency (primary analysis)	6 months	81.2% (225/277) [76.6, 85.8]	64.8% (92/142) [56.9, 72.6]	16.4% [7.3, 25.5]	<0.001
	12 months	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
	24 months	31.8% (49/154) [24.5, 39.2]	20.0% (17/85) [11.5, 28.5]	11.8% [0.6, 23.1]	0.047
DUS PSVR $\geq$ 3.0	6 months	83.5% (223/267) [79.1, 88.0]	72.1% (98/136) [64.5, 79.6]	11.5% [2.7, 20.2]	0.008
	12 months	68.3% (164/240) [62.4, 74.2]	56.1% (69/123) [47.3, 64.9]	12.2% [1.7, 22.8]	0.022
	24 months	33.6% (44/131) [25.5, 41.7]	23.9% (17/71) [14.0, 33.9]	9.6% [-3.2, 22.4]	0.150
DUS PSVR $\geq$ 2.5	6 months	81.5% (216/265) [76.8, 86.2]	65.7% (90/137) [57.7, 73.6]	15.8% [6.6, 25.0]	<0.001
	12 months	64.0% (155/242) [58.0, 70.1]	51.2% (65/127) [42.5, 59.9]	12.9% [2.3, 23.5]	0.017
	24 months	29.5% (41/139) [21.9, 37.1]	16.7% (13/78) [8.4, 24.9]	12.8% [1.6, 24.0]	0.032
DUS PSVR $\geq$ 2.0	6 months	70.1% (188/268) [64.7, 75.6]	54.8% (74/135) [46.4, 63.2]	15.3% [5.3, 25.4]	0.002
	12 months	53.2% (133/250) [47.0, 59.4]	45.0% (59/131) [36.5, 53.6]	8.2% [-2.4, 18.7]	0.130
	24 months	22.5% (36/160) [16.0, 29.0]	14.8% (13/88) [7.4, 22.2]	7.7% [-2.1, 17.6]	0.137

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value
Secondary Patency Rates	6 Months	86.2% (232/269) [82.1, 90.4]	71.2% (99/139) [63.7, 78.7]	15.0% [6.4, 23.6]	<0.001
	12 Months	75.9% (189/249) [70.6, 81.2]	68.3% (82/120) [60.0, 76.7]	7.6% [-2.3, 17.4]	0.126
	24 Months	65.9% (54/82) [55.6, 76.1]	56.4% (22/39) [40.8, 72.0]	9.4% [-9.2, 28.1]	0.317
DUS Clinical Patency	6 Months	81.2% (225/277) [76.6, 85.8]	65.5% (93/142) [57.7, 73.3]	15.7% [6.7, 24.8]	<0.001
	12 Months	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
	24 Months	31.8% (49/154) [24.5, 39.2]	20.2% (17/84) [11.6, 28.8]	11.6% [0.3, 22.9]	0.053
Freedom from Total TLR	6 Months	94.0% (280/298) [91.3, 96.7]	94.0% (142/151) [90.3, 97.8]	-0.1% [-4.7, 4.6]	0.973
	12 Months	87.7% (250/285) [83.9, 91.5]	83.2% (119/143) [77.1, 89.3]	4.5% [-2.7, 11.7]	0.208
	24 Months	73.3% (110/150) [66.3, 80.4]	64.1% (50/78) [53.5, 74.7]	9.2% [-3.6, 22.0]	0.151
Freedom from Clinically-Driven TLR	6 Months	94.0% (280/298) [91.3, 96.7]	95.4% (144/151) [92.0, 98.7]	-1.4% [-5.7, 2.9]	0.534
	12 Months	87.7% (250/285) [83.9, 91.5]	84.6% (121/143) [78.7, 90.5]	3.1% [-3.9, 10.1]	0.377
	24 Months	73.8% (110/149) [66.8, 80.9]	68.0% (51/75) [57.4, 78.6]	5.8% [-6.9, 18.5]	0.363
Device Success, % (n/N)	Procedural	99.5% (430/432)	100% (180/180)	-0.5%	0.361*
Technical Success (Core Lab, All Lesions), % (n/N)	Procedural	89.2% (282/316)	86.8% (138/159)	2.4%	0.431*
Procedural Success (Core Lab, All Lesions), % (n/N)	Procedural	88.9% (281/316)	86.8% (138/159)	2.1%	0.497*

* X_2-tests for proportions

Table 38. Secondary Efficacy Endpoint - Change in Index-limb Rutherford Classification (ITT Population)

	Test DCB				Control PTA			
Criteria[1]	**Baseline**	**6 Months**	**12 Months**	**24 Months**	**Baseline**	**6 Months**	**12 Months**	**24 Months**
Index-Limb Rutherford Classification								
0	0.0% (0/316)	52.8% (150/284)	51.7% (136/263)	51.7% (62/120)	0.0% (0/160)	49.7% (72/145)	42.7% (56/131)	46.3% (31/67)
1	0.0% (0/316)	22.5% (64/284)	24.0% (63/263)	25.8% (31/120)	0.0% (0/160)	20.7% (30/145)	28.2% (37/131)	23.9% (16/67)
2	29.4% (93/316)	11.6% (33/284)	15.6% (41/263)	11.7% (14/120)	34.4% (55/160)	12.4% (18/145)	13.7% (18/131)	23.9% (16/67)
3	62.7% (198/316)	10.9% (31/284)	6.8% (18/263)	10.8% (13/120)	57.5% (92/160)	16.6% (24/145)	14.5% (19/131)	6.0% (4/67)
4	7.9% (25/316)	1.8% (5/284)	1.9% (5/263)	0.0% (0/120)	8.1% (13/160)	0.0% (0/145)	0.8% (1/131)	0.0% (0/67)
5	0.0% (0/316)	0.4% (1/284)	0.0% (0/263)	0.0% (0/120)	0.0% (0/160)	0.7% (1/145)	0.0% (0/131)	0.0% (0/67)
Shift from Baseline								
Improved	N/A	86.3% (245/284)	88.2% (232/263)	86.7% (104/120)	N/A	81.4% (118/145)	82.4% (108/131)	89.6% (60/67)
1 class	N/A	17.3% (49/284)	20.2% (53/263)	16.7% (20/120)	N/A	14.5% (21/145)	19.1% (25/131)	25.4% (17/67)
2 classes	N/A	33.5% (95/284)	31.6% (83/263)	30.8% (37/120)	N/A	33.8% (49/145)	34.4% (45/131)	29.9% (20/67)
3 or more classes	N/A	35.6% (101/284)	36.5% (96/263)	39.2% (47/120)	N/A	33.1% (48/145)	29.0% (38/131)	34.3% (23/67)
Same	N/A	9.9% (28/284)	9.5% (25/263)	12.5% (15/120)	N/A	15.2% (22/145)	16.0% (21/131)	10.4% (7/67)
Worsened	N/A	3.9% (11/284)	2.3% (6/263)	0.8% (1/120)	N/A	3.4% (5/145)	1.5% (2/131)	0.0% (0/67)
1 class	N/A	3.5% (10/284)	2.3% (6/263)	0.8% (1/120)	N/A	2.8% (4/145)	1.5% (2/131)	0.0% (0/67)
2 classes	N/A	0.4% (1/284)	0.0% (0/263)	0.0% (0/120)	N/A	0.7% (1/145)	0.0% (0/131)	0.0% (0/67)

	Test DCB				Control PTA			
Criteria[1]	**Baseline**	**6 Months**	**12 Months**	**24 Months**	**Baseline**	**6 Months**	**12 Months**	**24 Months**
Summary at Visit	2.8 ± 0.6 (316) 3.0 (2.0, 4.0)	0.9 ± 1.1 (284) 0.0 (0.0, 5.0)	0.8 ± 1.0 (263) 0.0 (0.0, 4.0)	0.8 ± 1.0 (120) 0.0 (0.0, 3.0)	2.7 ± 0.6 (160) 3.0 (2.0, 4.0)	1.0 ± 1.2 (145) 1.0 (0.0, 5.0)	1.0 ± 1.1 (131) 1.0 (0.0, 4.0)	0.9 ± 1.0 (67) 1.0 (0.0, 3.0)
Change from Baseline	N/A	-1.9 ± 1.2 (284) -2.0 (-4.0, 2.0)	-1.9 ± 1.1 (263) -2.0 (-4.0, 1.0)	-2.0 ± 1.1 (112) -2.0 (-4.0, 1.0)	N/A	-1.8 ± 1.2 (145) -2.0 (-4.0, 2.0)	-1.7 ± 1.1 (131) -2.0 (-4.0, 1.0)	-1.9 ± 1.1 (67) -2.0 (-4.0, 0.0)

Table 39. Secondary Efficacy Endpoint - Change from Baseline of Index-limb resting ABI (ITT Population)

	Test DCB		Control PTA		Change from Baseline
Visit[1]	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
Baseline	0.74 ± 0.20 (306) 0.73 (0.00, 1.38)		0.73 ± 0.18 (156) 0.73 (0.00, 1.17)		
6 Months	0.93 ± 0.19 (280) 0.95 (0.00, 1.36)	0.20 ± 0.23 (274) 0.20 (-1.15, 0.91)	0.88 ± 0.18 (138) 0.90 (0.00, 1.33)	0.16 ± 0.22 (135) 0.16 (-0.88, 1.07)	0.04 ± 0.23 (-0.01, 0.09)
12 Months	0.91 ± 0.20 (264) 0.94 (0.00, 1.29)	0.17 ± 0.22 (258) 0.17 (-1.00, 0.78)	0.90 ± 0.23 (128) 0.94 (0.00, 1.38)	0.18 ± 0.25 (126) 0.17 (-0.88, 1.15)	-0.01 ± 0.23 (-0.06, 0.04)
24 Months	0.87 ± 0.20 (119) 0.92 (0.00, 1.33)	0.14 ± 0.25 (117) 0.14 (-0.67, 1.11)	0.90 ± 0.19 (65) 0.93 (0.41, 1.29)	0.16 ± 0.21 (63) 0.18 (-0.57, 0.69)	-0.02 ± 0.24 (-0.09, 0.06)

Table 40. Secondary Efficacy Endpoint - Change in Walking Impairment Questionnaire Score (ITT Population)

		Test DCB		Control PTA		Change from Baseline
Variable	**Visit**	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
WIQ total score[2]	Base-line	32.3 ± 23.2 (312) 28.8 (0.0, 100.0)		34.2 ± 23.1 (155) 32.3 (0.0, 96.0)		
	6 Months	59.3 ± 30.7 (283) 63.7 (0.3, 100.0)	26.6 ± 28.8 (280) 26.7 (-72.3, 95.0)	55.7 ± 32.6 (138) 59.7 (0.0, 100.0)	20.5 ± 28.7 (134) 20.7 (-60.0, 98.0)	6.0 ± 28.8 (0.1, 12.0)
	12 Months	57.3 ± 30.9 (264) 60.5 (0.0, 100.0)	23.9 ± 27.6 (261) 22.3 (-72.7, 95.0)	53.8 ± 31.1 (133) 57.7 (0.0, 100.0)	19.2 ± 26.5 (130) 16.5 (-65.3, 90.0)	4.7 ± 27.3 (-1.1, 10.4)
	24 Months	57.6 ± 29.7 (115) 60.0 (1.0, 100.0)	22.1 ± 29.7 (113) 18.7 (-50.3, 90.0)	52.9 ± 32.5 (66) 52.0 (0.0, 100.0)	18.3 ± 26.3 (65) 19.7 (-39.0, 74.3)	3.8 ± 28.5 (-5.0, 12.5)
Pain, aching or cramps in calves or buttocks score	Base-line	51.6 ± 26.8 (167) 50.0 (0.0, 100.0)		48.8 ± 28.5 (76) 50.0 (0.0, 100.0)		
	6 Months	78.0 ± 27.9 (180) 91.0 (0.0, 100.0)	26.4 ± 33.7 (111) 25.0 (-50.0, 100.0)	76.9 ± 26.1 (86) 83.0 (16.0, 100.0)	29.0 ± 18.1 (50) 25.0 (-9.0, 75.0)	-2.6 ± 29.8 (-12.7, 7.4)
	12 Months	78.7 ± 26.6 (165) 91.0 (0.0, 100.0)	25.9 ± 35.9 (98) 25.0 (-75.0, 100.0)	74.0 ± 29.8 (80) 87.0 (0.0, 100.0)	25.5 ± 34.3 (44) 25.0 (-58.0, 83.0)	0.4 ± 35.4 (-12.3, 13.1)
	24 Months	77.5 ± 26.4 (76) 83.0 (16.0, 100.0)	16.9 ± 37.0 (36) 21.0 (-67.0, 100.0)	76.9 ± 27.7 (38) 87.0 (8.0, 100.0)	36.2 ± 35.5 (19) 42.0 (-25.0, 92.0)	-19.3 ± 36.5 (-40.1, 1.4)
Walking distance score	Base-line	27.7 ± 26.3 (315) 20.0 (0.0, 100.0)		31.8 ± 26.2 (156) 26.5 (0.0, 100.0)		
	6 Months	61.0 ± 36.6 (286) 68.0 (0.0, 100.0)	33.3 ± 37.8 (286) 31.0 (-70.0, 99.0)	56.8 ± 37.9 (144) 66.0 (0.0, 100.0)	25.6 ± 36.3 (140) 23.0 (-98.0, 99.0)	7.6 ± 37.3 (0.1, 15.2)
	12 Months	60.0 ± 37.2 (266) 66.0 (0.0, 100.0)	31.5 ± 37.0 (266) 28.5 (-68.0, 99.0)	53.5 ± 36.5 (134) 55.0 (0.0, 100.0)	22.2 ± 35.4 (131) 21.0 (-79.0, 98.0)	9.3 ± 36.5 (1.6, 17.0)
	24 Months	61.4 ± 36.0 (119) 64.0 (0.0, 100.0)	30.1 ± 39.4 (119) 23.0 (-55.0, 99.0)	54.6 ± 37.7 (67) 52.0 (0.0, 100.0)	24.5 ± 39.0 (66) 18.0 (-72.0, 98.0)	5.7 ± 39.3 (-6.2, 17.6)
Walking speed score	Base-line	28.4 ± 24.0 (314) 25.0 (0.0, 100.0)		29.9 ± 26.0 (155) 25.0 (0.0, 100.0)		
	6 Months	52.7 ± 32.0 (285) 50.0 (0.0, 100.0)	24.1 ± 30.3 (284) 21.5 (-69.0, 100.0)	49.6 ± 32.8 (143) 50.0 (0.0, 100.0)	19.7 ± 30.5 (139) 15.0 (-82.0, 100.0)	4.3 ± 30.4 (-1.9, 10.5)
	12 Months	50.3 ± 31.3 (265) 50.0 (0.0, 100.0)	21.2 ± 29.0 (264) 18.5 (-51.0, 97.0)	48.0 ± 32.4 (134) 43.0 (0.0, 100.0)	17.7 ± 31.1 (131) 15.0 (-85.0, 84.0)	3.5 ± 29.7 (-2.7, 9.7)
	24 Months	49.8 ± 29.9 (117) 50.0 (0.0, 100.0)	18.4 ± 31.8 (116) 16.0 (-77.0, 100.0)	46.3 ± 31.1 (66) 39.5 (0.0, 100.0)	16.3 ± 28.4 (65) 15.0 (-54.0, 97.0)	2.1 ± 30.6 (-7.2, 11.5)

		Test DCB		Control PTA		Change from Baseline
Variable	**Visit**	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
Stair climbing score	Base-line	41.1 ± 30.6 (313) 38.0 (0.0, 100.0)		41.5 ± 30.7 (156) 40.0 (0.0, 100.0)		
	6 Months	64.0 ± 33.8 (283) 67.0 (0.0, 100.0)	22.0 ± 32.8 (281) 21.0 (-84.0, 100.0)	58.9 ± 35.3 (138) 67.0 (0.0, 100.0)	15.3 ± 34.6 (135) 9.0 (-67.0, 100.0)	6.7 ± 33.4 (-0.2, 13.5)
	12 Months	61.2 ± 34.0 (265) 67.0 (0.0, 100.0)	18.5 ± 33.6 (263) 13.0 (-100, 96.0)	59.6 ± 34.4 (133) 58.0 (0.0, 100.0)	17.4 ± 31.6 (131) 17.0 (-83.0, 100.0)	1.2 ± 32.9 (-5.7, 8.1)
	24 Months	61.2 ± 33.0 (116) 67.0 (0.0, 100.0)	16.1 ± 33.9 (115) 12.0 (-75.0, 83.0)	56.4 ± 35.9 (67) 54.0 (0.0, 100.0)	12.4 ± 29.2 (67) 9.0 (-55.0, 96.0)	3.6 ± 32.3 (-6.1, 13.4)

Table 41. Secondary Efficacy Endpoint - Change in Six-Minute Walk Test Distance (ITT Population)

	Test DCB		Control PTA		Change from Baseline
Visit	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
Base- line	306.3 ± 214.0 (301) 295.0 (15.0, 2191)		295.6 ± 136.5 (151) 300.0 (31.0, 1188)		
6 Months	357.2 ± 143.8 (276) 350.0 (49.0, 1122)	42.5 ± 205.7 (265) 45.0 (-1363, 877.0)	357.3 ± 207.2 (138) 342.5 (30.0, 1645)	61.1 ± 213.4 (131) 38.0 (-720, 1448)	-18.6 ± 208.2 (-62.3, 25.1)
12 Months	356.3 ± 152.0 (252) 360.0 (20.0, 1063)	45.0 ± 227.5 (244) 56.0 (-2019, 896.0)	341.9 ± 154.0 (125) 335.0 (16.0, 1206)	37.4 ± 171.7 (120) 38.0 (-784, 1014)	7.6 ± 210.8 (-38.6, 53.8)
24 Months	360.7 ± 113.8 (112) 360.0 (61.0, 878.0)	42.5 ± 177.3 (110) 36.0 (-970, 616.0)	387.3 ± 215.4 (62) 356.0 (118.0, 1128)	70.5 ± 259.3 (58) 22.5 (-773, 936.0)	-27.9 ± 209.1 (-94.9, 39.1)

Table 42. Secondary Efficacy Endpoint - Change in EQ-5D Index at 6, 12 and 24 Months (ITT Population)

	Test DCB				Control PTA			
Variable	**Baseline**	**6 Months**	**12 Months**	**24 Months**	**Baseline**	**6 Months**	**12 Months**	**24 Months**
EQ Index	0.73 ± 0.19 (301) 0.78 (0.17, 1.00)	0.81 ± 0.18 (277) 0.83 (0.17, 1.00)	0.82 ± 0.17 (263) 0.83 (0.11, 1.00)	0.80 ± 0.18 (105) 0.82 (0.16, 1.00)	0.71 ± 0.19 (154) 0.78 (0.20, 1.00)	0.81 ± 0.17 (143) 0.82 (0.27, 1.00)	0.79 ± 0.19 (131) 0.83 (0.20, 1.00)	0.81 ± 0.18 (60) 0.83 (0.31, 1.00)
Change from Baseline	N/A	0.08 ± 0.21 (265) 0.05 (-0.60, 0.69)	0.09 ± 0.20 (250) 0.05 (-0.70, 0.69)	0.05 ± 0.20 (97) 0.02 (-0.69, 0.54)	N/A	0.10 ± 0.18 (137) 0.05 (-0.36, 0.57)	0.08 ± 0.20 (127) 0.06 (-0.56, 0.52)	0.11 ± 0.19 (58) 0.12 (-0.40, 0.69)

[1] Summary is Mean ± SD (n) / median (min, max).

Table 43. Secondary Efficacy Endpoint - Change in SF-36 v2 Scores (ITT Population)

		Test DCB		Control PTA		Change from Baseline
Variable	**Visit**	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
Physical component summary	Base-line	35.7 ± 8.9 (315) 35.3 (-1.0, 60.1)		35.6 ± 10.2 (158) 36.6 (-1.0, 57.1)		
	6 Months	42.5 ± 11.0 (286) 42.9 (-1.0, 65.3)	6.6 ± 11.4 (286) 6.4 (-40.2, 46.6)	41.7 ± 11.4 (144) 41.9 (-1.0, 61.7)	6.3 ± 10.0 (142) 6.0 (-33.9, 39.6)	0.3 ± 10.9 (-1.9, 2.5)
	12 Months	42.1 ± 11.3 (263) 43.2 (-1.0, 65.3)	6.0 ± 11.4 (263) 5.9 (-43.8, 41.7)	40.8 ± 11.5 (134) 41.7 (-1.0, 60.6)	5.4 ± 10.2 (133) 5.2 (-24.4, 42.4)	0.6 ± 11.0 (-1.7, 2.9)
	24 Months	41.2 ± 10.9 (117) 41.9 (13.8, 60.2)	4.1 ± 11.5 (117) 4.1 (-21.7, 32.1)	40.9 ± 10.7 (65) 42.5 (18.6, 58.5)	5.0 ± 9.7 (65) 3.6 (-15.8, 38.1)	-0.9 ± 10.9 (-4.2, 2.4)

		Test DCB		Control PTA		Change from Baseline
Variable	**Visit**	**Raw**	**Change from Baseline**	**Raw**	**Change from Baseline**	**DCB-PTA Difference (95% CI)**
Mental component summary	Base-line	51.6 ± 12.6 (315) 53.7 (-1.0, 72.1)		50.7 ± 13.7 (158) 53.2 (-1.0, 72.2)		
	6 Months	51.2 ± 12.1 (286) 54.0 (-3.8, 72.2)	-0.7 ± 12.0 (286) -0.7 (-72.7, 49.3)	52.6 ± 10.8 (144) 55.6 (-1.0, 69.7)	1.6 ± 14.1 (142) 0.3 (-44.3, 59.3)	-2.3 ± 12.8 (-4.9, 0.2)
	12 Months	52.1 ± 11.7 (263) 55.1 (-1.0, 73.4)	0.2 ± 12.4 (263) -0.2 (-65.1, 53.2)	50.7 ± 12.4 (134) 53.9 (-1.0, 69.5)	0.4 ± 13.4 (133) -1.5 (-31.6, 59.2)	-0.2 ± 12.8 (-2.9, 2.5)
	24 Months	52.3 ± 11.9 (117) 55.9 (10.8, 74.9)	-0.1 ± 12.4 (117) 1.8 (-50.5, 36.7)	52.1 ± 11.9 (65) 54.5 (15.3, 69.8)	2.0 ± 12.6 (65) -0.8 (-24.1, 35.3)	-2.0 ± 12.5 (-5.8, 1.8)

[1] Summary is Mean ± SD (n) / median (min, max).

Table 44. Secondary Safety Endpoints by Timepoint (ITT Population)

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value2
VIVA[2] Safety Endpoint at 1 Month	1 Month	99.7% (307/308) [99.0, 100.0]	99.4% (154/155) [98.1, 100.0]	0.3% [-1.1, 1.7]	0.630
Freedom from Composite Safety Events[1]	1 Month	99.4% (306/308) [98.5, 100.0]	99.4% (154/155) [98.1, 100.0]	-0.0% [-1.6, 1.5]	0.996
	6 Months	92.0% (275/299) [88.9, 95.1]	91.4% (138/151) [86.9, 95.9]	0.6% [-4.8, 6.0]	0.832
	12 Months	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-3.0, 12.8]	0.215
	24 Months	68.2% (107/157) [60.9, 75.4]	56.8% (46/81) [46.0, 67.6]	11.4% [-1.7, 24.4]	0.085
All-cause Death	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.7% (2/301) [0.0, 1.6]	1.3% (2/152) [0.0, 3.1]	-0.7% [-2.7, 1.4]	0.497
	12 Months	2.4% (7/290) [0.6, 4.2]	2.8% (4/144) [0.1, 5.5]	-0.4% [-3.6, 2.8]	0.822
	24 Months[3]	6.9% (10/144) [2.8, 11.1]	6.6% (5/76) [1.0, 12.2]	0.4% [-6.6, 7.3]	0.918
CEC Adjudicated Index-Limb Related Death	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.0% (0/301) [0.0, 0.0]	0.0% (0/152) [0.0, 0.0]	0.0%	N/A
	12 Months	0.0% (0/290) [0.0, 0.0]	0.0% (0/144) [0.0, 0.0]	0.0%	N/A
	24 Months[3]	0.0% (0/144) [0.0, 0.0]	0.0% (0/76) [0.0, 0.0]	0.0%	N/A
Major Amputation	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.3% (1/299) [0.0, 1.0]	0.0% (0/151) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.366
	12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.372
	24 Months	0.7% (1/135) [0.0, 2.2]	0.0% (0/71) [0.0, 0.0]	0.7% [-0.7, 2.2]	0.357

Minor Amputation	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.0% (0/298) [0.0, 0.0]	0.0% (0/151) [0.0, 0.0]	0.0%	N/A
	12 Months	0.0% (0/285) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]	0.0%	N/A
	24 Months	0.0% (0/134) [0.0, 0.0]	0.0% (0/71) [0.0, 0.0]	0.0%	N/A
Total TVR	1 Month	0.3% (1/308) [0.0, 1.0]	0.6% (1/155) [0.0, 1.9]	-0.3% [-1.7, 1.1]	0.630
	6 Months	6.7% (20/298) [3.9, 9.6]	7.9% (12/151) [3.6, 12.3]	-1.2% [-6.4, 3.9]	0.633
	12 Months	13.3% (38/285) [9.4, 17.3]	18.2% (26/143) [11.9, 24.5]	-4.8% [-12.3, 2.6]	0.190
	24 Months	28.3% (43/152) [21.1, 35.4]	39.2% (31/79) [28.5, 50.0]	-11.0% [-23.9, 2.0]	0.093
Reintervention for Thrombosis	1 Month	0.3% (1/308) [0.0, 1.0]	0.0% (0/155) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.366
	6 Months	0.3% (1/298) [0.0, 1.0]	0.7% (1/151) [0.0, 2.0]	-0.3% [-1.8, 1.1]	0.633
	12 Months	0.4% (1/285) [0.0, 1.0]	0.7% (1/140) [0.0, 2.1]	-0.4% [-1.9, 1.2]	0.618
	24 Months	0.7% (1/135) [0.0, 2.2]	1.4% (1/71) [0.0, 4.1]	-0.7% [-3.8, 2.4]	0.651

Major Vascular Complications[4]	1 Month	4.2% (13/308) [2.0, 6.5]	1.3% (2/156) [0.0, 3.0]	2.9% [0.1, 5.8]	0.068
	6 Months	5.4% (16/298) [2.8, 7.9]	2.6% (4/152) [0.1, 5.2]	2.7% [-0.9, 6.3]	0.164
	12 Months	6.3% (18/285) [3.5, 9.1]	4.9% (7/142) [1.4, 8.5]	1.4% [-3.2, 5.9]	0.560
	24 Months	13.6% (20/147) [8.1, 19.1]	10.7% (8/75) [3.7, 17.7]	2.9% [-6.0, 11.9]	0.528
Cardiovascular Hospitalization	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	5.7% (17/298) [3.1, 8.3]	2.0% (3/151) [0.0, 4.2]	3.7% [0.3, 7.2]	0.054
	12 Months	9.1% (26/285) [5.8, 12.5]	7.1% (10/140) [2.9, 11.4]	2.0% [-3.4, 7.4]	0.485
	24 Months	25.5% (38/149) [18.5, 32.5]	25.3% (20/79) [15.7, 34.9]	0.2% [-11.7, 12.1]	0.975

Table 45. Other Secondary Endpoints by Timepoint (ITT Population)

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value2
Target limb related hospital days at 1 and 2 years	12 Months	Not Available Admission and discharge dates were not captured in the eCRF or monitored. Analysis will be reported in the 24 month Report.			
	24 Months				
Primary Patency Rate by Kaplan-Meier	30 days	94.9% [91.8, 96.8]	93.7% [88.6, 96.6]	1.20%	0.0205
	183 days	88.8% [84.7, 91.9]	78.5% [71.1, 84.2]	10.20%	
	365 days	73.5% [68.0, 78.2]	56.8% [48.3, 64.4]	16.70%	
	730 days	53.7% [45.3, 61.3]	48.4% [37.7, 58.3]	5.30%	
DUS Clinical Patency by Kaplan Meier	Not performed – Essentially the same as primary patency by Kaplan Meier.				

Freedom from Composite Safety Events by Kaplan-Meier	30 days	99.4% [97.5, 99.8]	99.4% [95.6, 99.9]	0.00%	0.1125
	183 days	94.0% [90.7, 96.2]	94.1% [88.9, 96.9]	-0.10%	
	365 days	86.7% [82.3, 90.1]	81.5% [74.1, 86.9]	5.20%	
	730 days	80.6% [75.0, 85.1]	72.6% [63.5, 79.8]	8.00%	
Freedom from TLR by Kaplan-Meier	30 days	99.7% [97.8, 100.0]	100.0% [N/A]	-0.30%	0.1673
	183 days	96.0% [93.1, 97.7]	96.0% [91.3, 98.2]	-0%	
	365 days	89.7% [85.7, 92.7]	84.8% [77.8, 89.7]	4.90%	
	730 days	84.1% [78.7, 88.3]	78.1% [69.5, 84.6]	6.00%	

Appendix 2: Defintions

Acute Technical Success
Acute technical success is defined as, a per device basis, the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion, without residual dissections, without visible thrombus, without "watermelon seeding" of the balloon, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system.

All Cause Perioperative Death
All-cause Perioperative Death is defined as death within 30 days of the index procedure.

Amputation of the Index Limb
Amputation includes all amputations including both Major Amputations (above the ankle) and Minor Amputations (including amputations below the ankle).

Ankle Brachial Index Assessment
Ankle systolic pressure/brachial systolic pressure, measured by constructing a ratio from the peak systolic pressure measured during the deflation of the ankle cuffs during Doppler detection to the systolic brachial pressure.

As-Treated
The As-Treated analysis is based only on those subjects treated with either an investigational or control device, and the comparison is based on the actual device used, not randomized assignment.

Binary Restenosis Rate
The presence of a hemodynamically significant restenosis (>50%) as determined by angiography or by duplex ultrasound (defined by systolic velocity ratio≥2.5).

Clinically Driven Target Lesion Revascularization
Revascularization at the target lesion with evidence of target lesion diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb).

Clinically Driven Target Vessel Revascularization
Revascularization of the target vessel with evidence of diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb).

DUS Clinical Patency
Defined as patency of the target limb (based on a PSVR threshold < 2.5) without prior Clinically Driven TLR.

Device Malfunction
A malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Device Success
Acute technical success is defined as, a per device basis, the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system. If a device is inserted into the subject but not used due to user error (e.g. inappropriate balloon length or transit time too long), this device will not be included in the device success assessment.

Dissections
National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:
0: None
A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.
D. Spiral luminal filling defects.
E. New persistent filling defects.
F. Non-A-E types that lead to impaired flow or total occlusion.
Note: Type E and F dissections may represent thrombus.

Enrollment
The point at which the subject has met all the study inclusion and none of the study exclusion criteria, the guidewire has been placed across the study lesion and study pre-dilatation has occurred.

Intent-To-Treat (ITT)
The principle of including outcomes of all subjects in the analysis who are randomized into the study, regardless of the treatment actually received.

Index Limb Related Death
Any death adjudicated by the DMC as “likely related” to a complication of the index limb.

Major Bleeding Complications
Bleeding will be considered major if:

- It leads to death;
- It leads to permanent disability;
- It is clinically suspected or proven to be intracranial (see stroke)
- It produces a fall in hemoglobin of at least 3 mmol/l;
- It leads to transfusion of 2 or more units of whole blood of packed cells;
- Peripheral vascular surgery is necessary.

- All other bleeding will be considered as minor.

Major Vascular Complications
Hemorrhagic vascular complications included the following:
- Haematoma at access site >5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury
- Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication
- Vascular surgical repair

Patent Run-off
At least one patent native outflow artery from the popliteal to the ankle, free from significant (≥50%) stenosis as confirmed by angiography or ultrasound that has not previously been revascularized.

Per-Protocol (PP)
The PP analysis is based on all subjects that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), availability of measurements, and the absence of major protocol violations including violations of entry criteria.

Primary Patency
Primary Patency of the target lesion is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio ≥2.5 (or based on angiography if performed), as analyzed by independent core lab, without prior target lesion revascularization. (Alternative Primary Patency is also reported PSVR thresholds ≥2.0 and ≥3.0.)

Procedural success
Attainment of ≤30% residual stenosis in the treatment area by independent core lab analysis without major adverse events during the index procedure.

Popliteal Artery
The vessel located between Hunter's canal and the trifurcation.

PSVR
Peak Systolic Velocity Ratio

Reference Vessel Diameter (RVD)
The interpolated reference vessel diameter is based on a computed estimation of the original diameter of the artery at the level of the obstruction (minimal luminal diameter)

Restenosis
Either ≥50% restenosis of the diameter of the reference-vessel segment by QVA or peak systolic velocity ratio of ≥2.5, determined by blinded ultrasound and independent core lab analysis.

Restenotic Lesion

A lesion in a vessel segment that had undergone a prior percutaneous treatment

Rutherford Categories

Grade	Category	Clinical Description	Objective Criteria
	0	Asymptomatic, no hemodynamically significant occlusive disease	Normal results of treadmill (5 min,2 mph, 12^0 constant grade)
I	1 2 3	Mild Claudication	Treadmill exercise complete, post exercise AP is greater than 50 mm Hg but more than 25 mm Hg less than normal
		Moderate Claudication	Symptoms between categories 1 and 3
		Severe Claudication	Treadmill exercise cannot be completed post exercise AP is less than 50 mm Hg
II	4	Ischemic rest pain	Resting AP of 40 mm Hg or less, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure less than 30 mm Hg
III	5 6	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia	Resting AP of 60 mm Hg or less, flat or barely pulsatile ankle metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure less than 40 mm Hg
		Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

Screen Failures

Subjects screened, but not meeting all study entry criteria and hence are not enrolled, are considered screening failures and will be documented as such on the Screening Logs.

Secondary Patency

Secondary Patency of the target lesion is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio ≥2.5 (or based on angiography if performed) as analyzed by independent core lab, independent of whether or not patency is re-established via an endovascular procedure.

Stroke

Clinical signs/symptoms of focal neurological deficit lasting longer than 24 hours.

Target Lesion
Lesion that is to be treated during the index procedure. For study inclusion, the lesion must be ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the posterior tibial trunk, with the intent of staying above the trifurcation.

Target Lesion Revascularization
A repeat revascularization procedure (percutaneous or surgical) of the original target lesion site.

Target Vessel Revascularization
A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel.

Target Vessel
The entire vessel in which the target lesion is located.

Technical Success
Technical Success of the balloon procedure is defined as successful access and deployment of the device and visual estimate of ≤30% diameter residual stenosis during the index procedure without deployment of a bailout stent.

Treatment Area
The entire treated vessel segment in which angioplasty balloons were inflated (the injury segment)
including the target lesion.

Thrombosis
A total occlusion documented by duplex ultrasound and/or angiography at the treatment site with or without symptoms Thrombosis may be categorized as acute (<1 day), subacute (1-30 days) and late(>30 days). The presence of thrombus at the target lesion must be noted as an adverse event in the eCRF.

Transient Ischemic Attack (TIA)
Clinical signs/symptoms of focal neurological deficit lasting up to 24 hours

Walking Impairment Questionnaire (WIQ)
A measure of subject-perceived walking performance for subjects with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed and stair climbing capacity.

Worsening of Ankle Brachial Index
A deterioration in the Ankle Brachial Index (ABI) by more than 0.15 from the maximum early post-procedural level.

Worsening Rutherford Clinical Category

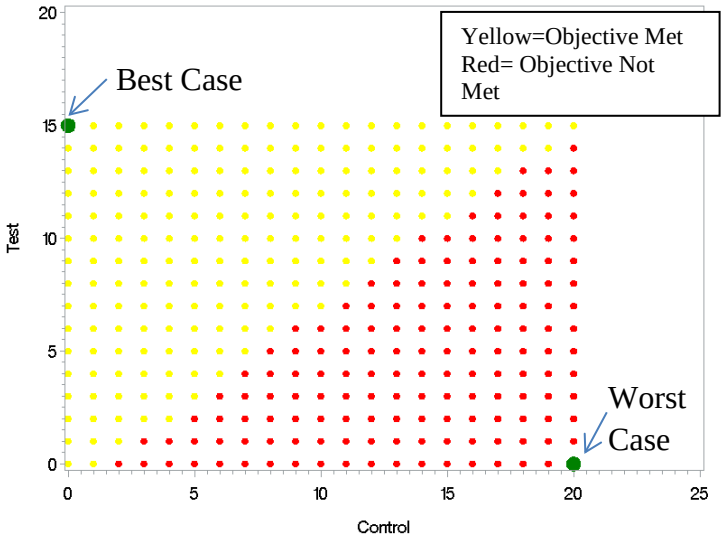
A deterioration (an increase) in the Rutherford Category by more than 1 category from the earliest post-procedural measurement.

Appendix 3: Explanation of Tipping Point Analyses

Tipping point analysis is a non-model based approach to handle missing data issue. Tipping point analysis tests whether the null hypothesis would be rejected if each combination of missing endpoints between the test and the control groups was observed. Suppose the endpoint of interest is a binary endpoint (success vs. failure). Then the best-case scenario would be if all missing endpoints in the test group were successes, but that all missing endpoints in the control group were failures. On the other hand, the worse-case scenario would be if all missing endpoints in the test group were failures, but the all missing endpoints in the control group were successes.

To illustrate, the figure below shows an example of tipping point analysis. The X-axis represents the number of successes out of missing endpoints in the control group, and the y-axis represents the number of successes out of missing endpoints in the test group. The region in red represents all of the possible combinations of successes between the test and the control groups at which the null hypothesis would not be rejected (**objective not met**); whereas the region in yellow represents all the possible combinations of number of successes at which the null hypothesis is rejected (**objective met**).

Figure Tipping Point Analysis (example)



Suppose both the test and the control group have sample size of 100; there were 15 and 20 missing endpoints in the test and control groups, respectively; and the success rate was 90.6% (=77/85) for the test group and 85.0% (=68/80) for the test group. Then the best-case scenario would be if all 15 missing endpoints in the test group were successes (77+15=92 out of 100

success) and all 20 missing endpoints in the control group were failures (68+0=68 out of 100 successes). This combination is presented as the green dot in the upper-left corner of the figure. Similarly, the worse-case scenario would be if all 15 missing endpoints in the test group were failures (77 out of 100 successes) and all 20 missing endpoints in the control group were successes (68+20=88 out of 100 successes). This combination is presented as the green dot in the lower-right corner of the figure.